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The mission of the Journal of the Malta College of Family Doctors (JMCFD) is to deliver accurate, relevant and inspiring research, continued medical education and debate in family medicine with the aim of encouraging improved patient care through academic development of the discipline. As the main official publication of the Malta College of Family Doctors, the JMCFD strives to achieve its role to disseminate information on the objectives and activities of the College.

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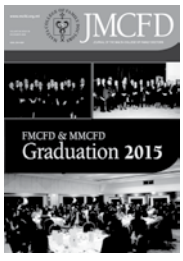

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Collegiality, philanthropy and research

Prof. Pierre MALLIA

The 25th Anniversary marks a special occasion for the MCFD. In this issue we reproduce some photos taken from the Gala Dinner organised at the Corinthia Palace Hotel, Attard on the 27th October 2015 (see pages 16-17). For the occasion the Council issued a call to confer the first Fellowships. It is only proper that one should not allow such a landmark to pass without launching and re-thinking the objectives of the College to meet its ultimate aim. The occasion also incorporated the annual MMCFD graduation and we also gave a memento to invited guests and past council members (see names of graduates and past council members on the next page).

First and foremost the collegiate nature of the MCFD gives us the responsibility for not only seeing to our own continuing medical education and professional development but, since the agreement with the Royal College of General Practitioners, the preparation of newly qualified doctors who choose to pursue a career in this noble speciality. Being listed on the specialist register is not something to be taken lightly and we marked the event when the Specialist Accreditation Committee (SAC) was set up by striving to have a vocational training programme with a summative assessment which includes Work-Based Assessment, a Clinical Skills Examination and an Applied Knowledge Test. Passing this examination allows one to be a member of the MCFD which then confers the right to apply for the international MRCGP(INT) – a contextual post-graduate qualification. The College has come far in its education programme and we now hope to extend this qualification to existent members on the specialist register. We are collaborating with the Royal College of General Practitioners (RCGP) to have a CME programme which will be recognized, and which will hopefully serve us well when the Medical Council instils a re-validation programme (which should be based on a CME programme). The RCGP have said they will insist on sitting for the AKT exam, but this should not be a problem for many as it is based on questions which a reasonably safe doctor ought to know.

The Fellowship of the College is an award which honours doctors who have spent at least five years of their professional lives contributing to the College in some way or another. These people have shown an interest in Family Practice beyond their immediate practices – an interest which is not profit-oriented and which has contributed to the advancement of doctors and quality of care. This bring me to the second important role that the MCFD plays – a role on which we will focus over the next three years – our *philanthropic* one.

Philanthropy involves caring, nourishing and enhancing something for humanity. In our case it is good health care for patients. This is oriented not only to the benefactors themselves (which in our case are the College members) but also the beneficiaries – our patients. Of course one may argue that we do this already by improving the quality of care. We are now however moving towards the new international paradigm as seeing the patient as partner in developing knowledge, education, and research. The idea is not only to impart knowledge which we feel patients ought to know but to respond to patient groups' need in this regard. A group for a particular condition will have needs which we can help address. Our role as patient advocates may help develop our policies in order to give a push to political changes which are necessary. This is already done on an individual level by many doctors, who participate or even preside over some patient groups. We can now move more collectively and deal with groups like the Malta Health Network (an umbrella organisation for patient groups), Hospice Malta, the 'Kunsill Nazzjonali Persuni b' Diżabilità (KNPD), etc. Patients can address to us areas which can allow us to generate research questions in family medicine and general practice which are relevant also to patients and which can help in various

ways. Research can therefore be more targeted and can participate in broader goals.

The philanthropic role is also extended internationally and the RCGP sees us as potential helpers in developing family medicine in countries around the Mediterranean. We have already helped Kosovo develop their speciality to an extent and have supported doctors in Libya by accrediting some courses. We will continue to do this and find robust ways of doing so rather than responding to immediate requests.

An aim which will be put forward to the next council is a facilitation of research and participation of our members in EU projects in family medicine in which they wish to be partners. We hope to have a legal framework in place so that any member wishing to apply for an EU project will find the necessary support and structure necessary for this. One experience that we had in applying for an Erasmus project showed that this cannot be handled by council members who already have a lot on their plates (unless of course they want to). Rather any member can apply for his or her own project and advice and legal support will be given in this regard. One needs to be in an organisation which takes legal responsibility and audit and the funds one obtains can certainly pay for this in order for projects to be won by individuals representing the College. These funds will allow researchers to be paid for their work as well. We look towards Horizon 2020 along with other large Colleges around Europe. Indeed members from these colleges can serve as partners.

This is the last issue before the election of the new council. I wish to personally thank (as President and not as editor) all members of council who deserve your utmost regard for the excellent work they do. We meet in evening and things are not always plain sailing. I therefore not only thank the following doctors but also their spouses and families without whose support they would not be working for you: Dr. Philip Sciortino, Dr. Jason Bonnici, Dr. Marco Grech, Dr. Doreen Cassar, Dr. Tania van Avendonk, Dr. Jean Pierre Cauchi, Dr. Edward Zammit, Dr. Daryl Xuereb, and Dr. Adrian Micallef. I also thank Drs. Patricia DeGabriele and Dominic Agius who also served for a while on this council.

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Fibular stress fracture in a female cross-country runner: a case report

Dr Matthew PSAILA, Dr Kirill MICALLEF STAFRACE

ABSTRACT

Introduction

Stress fractures are probably the most feared class of injuries amongst endurance athletes, especially runners, since they require lengthy rehabilitation periods and temporary but drastic modifications of their training regime. A detailed literature review is presented with the aim of highlighting the importance of athlete education as well as pre-participation screening in female athletes for one or more components of the triad.

Case Presentation

The case of a female adolescent cross-country runner is presented. Her only complaint of note prior to being reviewed at the clinic was of bilateral anterior shin pain during running that was dismissed by herself and her coach as being shin splints. The patient was not limited by these symptoms and managed to persist with her training regime. She was referred for review by a medical professional after she felt excruciating pain in her right lower leg associated with swelling during a race. Following a detailed history and examination, a plain X-Ray confirmed the presence of a complete transverse fracture of the shaft of her right fibular bone. X-Rays of the unaffected limb were not taken.

Conclusion

Although the case presented depicts a possible complication of the female athlete triad, confirmation of the presence or absence of the triad (disordered eating, amenorrhea amd osteoporosis) could not have been made in view of the omission of essential investigations. The case serves to raise the notion of pre-empting through earlier assessment and exercise modification with particular attention to all three components of the triad. Nonetheless, despite an increased risk of sustaining musculoskeletal injuries during physical activity, the safe participation in physical activity that is preceded by pre-participation screening, benefits the long-term health of girls and women and should be encouraged.

Keywords

Female triad, fibular fracture, screening, energy balance

INTRODUCTION

The American College of Sports Medicine (ACSM) described the association of disordered eating, amenorrhea and osteoporosis as the female athlete triad, which is especially prominent in sporting disciplines emphasizing a lean physique (Nattiv *et al.,* 2007). Although interrelated, the simultaneous occurrence of all three components in a female subject is rare. Lauder and colleagues (1999) failed to identify the simultaneous presence of all three components in a study of 423 female military personnel (Lauder *et al.,* 1999) whilst Nichols and colleagues (2006) in their study of high-school athletes identified all three components in only 2 of 170 screened athletes (Nichols *et al.,* 2006). Furthermore, although frequently described in the literature with reference to athletes, any of the components of the triad may occur in non-athletes (Torstveit and Sundgot-Borgen, 2005).

CASE REPORT

Background

A case is presented of an adolescent female cross-country runner who had been selected by the Maltese National Olympics Committee (MOC) to compete in a 3.5 kilometre run that was scheduled to take place in six months time. Consent for presenting this case report was sought by the authors from the patient. Furthermore, the case and the accompanying images have been anonymised.

The patient had attained the standards required by the MOC over a span of six months, prior to which she did not undertake physical training (including running) on a regular basis and according to a structured training programme. Prior to starting her training, she was given a medical screening form which had to be filled in by her General Practitioner to notify her trainers and coaches of

any medical conditions of note. It is important to note that her dietary and menstrual history was not taken into consideration in this screening form. Furthermore at no point was a nutritionist asked to review the athlete's dietary intake.

The athlete followed her training regime meticulously and was progressing as planned. She was advised to start a two hour per week running programme (mostly conducted on asphalted surfaces) increasing by 45 minutes every three to four weeks to a maximum of four hours per week. Apart from running exercises she also participated in interval training with variable running speeds. She was also undertaking core stability exercises during her rest days and was making an effort to improve her nutritional intake. Despite this, her diet remained lacking in dairy and meat products (especially red meat) and she was not on any regular food supplements. Her dietary habits were not precipitated by her desire to lose weight or because of a distorted bodily image but rather because eating was not a priority for her with most of her time being dedicated for physical training.

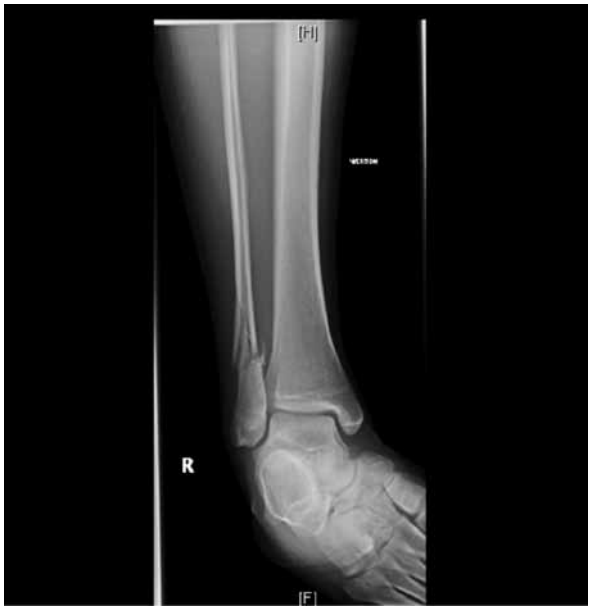

Figure 1: X-Ray, antero-posterior view of the right ankle held in inversion showing a comminuted fracture of the distal third of the right fibular bone (Day 0)

History of Presenting Complaint

She first noticed the onset of bilateral lower medial shin pain, worse on her right leg, during the first three months of regular training. She described this as a nagging pain that did not limit her in her running. Her symptoms were provoked by running and stopped without the need of any treatment soon after she finished her training. In view of an increasing frequency of these episodes she consulted a physiotherapist who advised changing her running technique, strapping and calf stretching exercises. Despite this the pain still persisted. She described that the intensity of the pain was highest two days before her 3.5 kilometre run, being associated with some swelling over her right lower leg. She did not seek medical advice for fear of being advised to withdraw from the race.

Diagnosis and management

A few minutes into the race, the athlete recalled feeling a sudden increase in pain over her right lower leg compared to the sensation of being kicked in her shin. Despite this she managed to persist with the race and managed also to sprint the last 500 metres of the race. On crossing the finish line she was in severe pain and also noticed a significant amount of swelling over her right lower leg. She was reviewed by a sports physician later in the day who in the context of a history of shin splints, probable sub-optimal calorie intake and the presence of pes-planus on examination made a preliminary diagnosis of stress fracture of her right tibia. It is important to note that the athlete did not give a history of menstrual irregularity.

After undertaking a plain X-ray of her right leg, she was found to have a complete comminuted fracture of the lower distal third of the shaft of her right fibula (Figure 1). This was surprising considering that her symptoms were always located over the anterior surface of her right lower tibia. Her right leg was immobilized in plaster and she was asked to attend for review after 6 weeks (Figure 2). Since the patient's fracture was complicated by delayed union (as evident in Figure 3 representing a radiographic image taken nine weeks after her injury), blood tests were taken to assess nutritional status. At no point in her management was a Bone Mineral Density (BMD) assessment performed. She was prescribed iron and calcium tablets, customized insoles (as prescribed by a podiatrist) and advised to optimize her dietary intake of calcium and iron-rich foods.

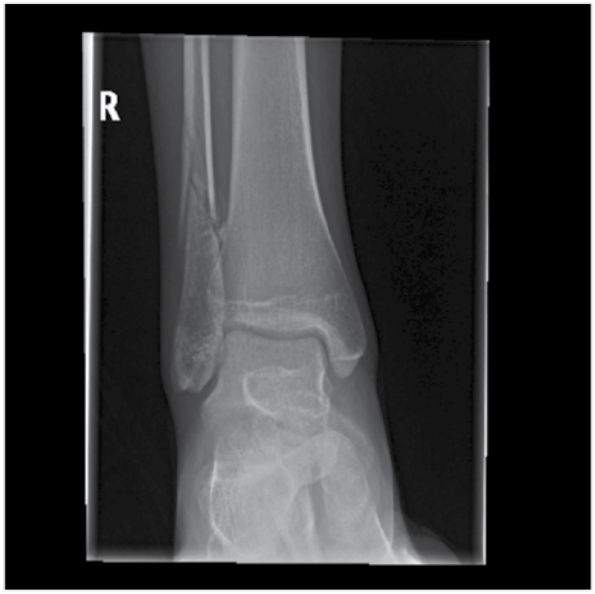

Figure 2: X-Ray, antero-posterior view of the right ankle showing satisfactory alignment of the fracture of the distal third of the right fibular bone (Day 40)

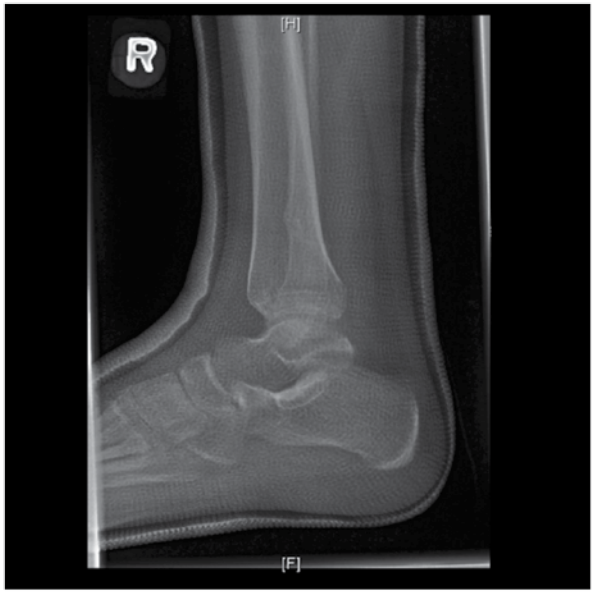

Figure 3: X-Ray, lateral view of the right ankle in plaster showing satisfactory alignment and callous formation at week 9 of the fracture of the distal third of the right fibular bone (Day 68)

DISCUSSION

Mechanism

The negative energy balance resulting from inadequate dietary intake to compensate for the increasing energy expenditure from physical training results in physiological interruption of bodily functions not deemed essential for survival, including reproduction (Wade *et al.,* 1996). The resulting disruption of the hypothalamic-pituitary-gonadal axis from the ensuing negative energy balance leads to hormonal imbalance, menstrual irregularity including amenorrhea, defined as the absence of menses for three or more months (American Society for Reproductive Medicine, 2004). Menstrual irregularities are associated with lower BMD scores in adolescent athletes (Drinkwater *et al.,* 1990) which is an independent risk factor for stress fractures (Bennell *et al.,* 1999).

Apart from affecting BMD indirectly through a decrease in estrogen levels, which as a hormone reduces bone resorption, a negative energy balance may also directly result in reductions in BMD scores through metabolic hormones which promote bone formation – see Figure 4 (Nattiv *et al.,* 2007). Endurance training in an athlete in chronic negative energy balance was found by Zanker and Swaine (2000) to reduce levels of insulin-like growth factor-1 (Zanker and Swaine, 2000). The latter peptide hormone is known to promote bone formation (Rosen, 1999).

Screening

The female athlete triad coalition is a group of representatives from a number of sporting and medical organizations who formulated a pre-participation questionnaire (listed in Table 1 hereunder) for female subjects spanning disordered eating, menstrual dysfunction and bone health (Mencias *et al.,* 2012). Rather than being suggested for use as a questionnaire it represents suggestions of questions that the physician should ask during history taking to recognize at-risk athletes. The information obtained coupled with the physical examination may guide requests for investigations which may include BMD testing (Nattiv et al., 2007).

Despite the ACSM recommendations of BMD testing in female subjects after six months of menstrual irregularity, in a study by Pollock and colleagues (2010) of BMD scores in elite athletes, no significant differences were found between athletes with regular menses and those with irregular menses (Pollock *et al.,* 2010). In the latter study, however, reproductive hormones were not analysed and therefore athletes with menstrual irregularities secondary to pathology other then that caused by the functional hypothalamic amenorrhea seen in the female athlete triad, may have been recruited. Furthermore, some of the athletes with menstrual irregularity were taking the oral contraceptive pill which may affect BMD scores (Cobb *et al.,* 2007)

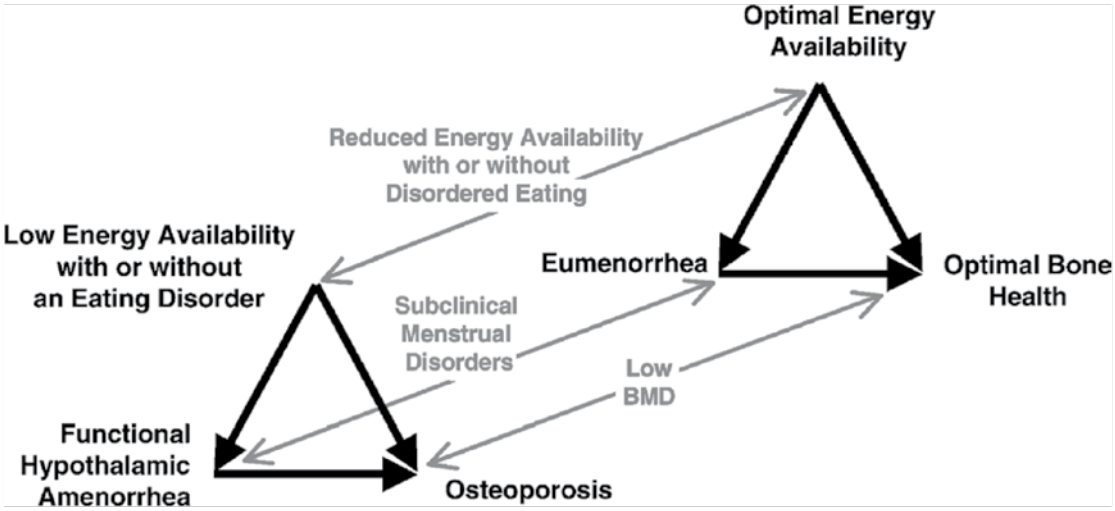

Figure 4: Spectrums of energy availability, menstrual function and BMD forming the female athlete triad. BMD, Bone Mineral Density (Nattiv ***et al.***, 2007).

Spectrum	Suggested questions
Disordered eating	
	Do you worry about your weight?
	Do you limit the foods you eat?
	Do you lose weight to meet image requirements for your sport?
	Does your weight affect the way you feel about yourself?
	Do you feel you have lost control over what you eat?
	Do you make yourself vomit; use diuretics or laxatives after you eat?
	Have you ever suffered from an eating disorder?
	Do you ever eat in secret?
Menstrual dysfunction	
	What age was your first menstrual period?
	Do you have monthly menstrual cycles?
	How many menstrual cycles have you had in the last year?
Bone health	
	Have you ever had a stress fracture?

Table 1: Recommended questions by the Female Athlete Triad Coalition for the purpose of screening on pre-participation forms (Mencias 2012).

Summary and relevance of above to the case

The presented case highlights one of the components of the female athlete triad, that is disordered eating, which combined with the rapid progression in her training regime and biomechanical errors missed during screening, resulted in a stress fracture. Further assessment of all components of the female triad, with BMD calculation and accurate energy input and output charting, have unfortunately been omitted from this case by the managing medical team. Therefore, despite the aim of the presented case to raise awareness regarding the female triad, it cannot be concluded with certainty whether the presented case is in fact secondary to the female triad. Confirmation of the presence or absence of the female triad is clinically important since management of all components of the triad would require the input of a multidisciplinary team.

A further point of interest in this case is pain distribution on presentation, that is, the distal anteromedial surface of the leg which is not typical of a fibular fracture. The latter might be suggestive of injury to the anterior talofibular ligament (high ankle sprain); however, specialized testing and/or imaging to confirm or exclude this injury were not performed. The fibular bone plays a minimal role in weight bearing and in fact, fibular fractures should lead the medical professional to screen for associated biomechanical errors, which in the presented athlete's case were excessive pronation and soft tissue tightness (Wilder and Sethi, 2004).

CONCLUSION

This case highlights the importance of recognizing the early warning signs of an impending stress fracture as well as the investigations which may be considered in female athletes at risk of the female triad. This screening should go hand in hand with a full medical history inclusive of a dietary and menstrual history to identify issues which may need addressing before an athlete engages in regular physical training. The latter can be facilitated further by using a questionnaire as listed above, as well as with the involvement as necessary of a multidisciplinary team comprising of physiotherapists, nutritionists and physical trainers. Screening should be repeated at follow-up sessions to reaffirm the initial advice and help identify early warning signs of the triad. Furthermore, since the number of women participating in sports is increasing, coaches, trainers and the athletes themselves should be informed on the particular risks faced by female athletes as elucidated by the female athlete triad.

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Obesity and sedentary behaviour in children and their implications in adulthood

Dr Mario SALIBA

ABSTRACT

The problem of childhood overweight and obesity are becoming more prevalent. Sedentary behaviours and the lack of physical activity are considered as independent health risk factors. The commoner chronic illnesses in adults such as obesity, high blood pressure, diabetes, and cancer are aggravated by a sedentary life. The evidence strongly suggests that sedentary behaviour is correlated to obesity in childhood and can negatively affect health in early adulthood. A literature review about the problem of childhood obesity and sedentary behaviour in children and their implications in adulthood is discussed. Efforts should be made to introduce specific interventions to increase physical activity among children and decrease sedentary behaviour such as television viewing and using electronic media. Campaigns and training programmes for parents should be implemented.

Key words

Physical activity, sedentary behaviour, children, obesity, health risk, adulthood.

INTRODUCTION

Sedentary behaviour has been defined as activities requiring low levels of energy expenditure that include sitting or lying down (Atkin et al., 2012). But sedentary behaviour is not simply that time spent just doing nothing but it is the product of time spent in specific sedentary behaviours (Jago et al., 2010). There is increasing interest in sedentary behaviours as an independent health risk factor. Physical activity or the lack of it may affect mental and physical development (Durnin, 1989).

The problem of childhood overweight and obesity is very common in many western European countries (Wang and Lobstein, 2006). According to a study by Grech et al. (2006) obesity among children in the Maltese Islands is the greatest current national health crisis and this problem must be addressed with urgency. In a study conducted by Decelis et al. (2012) it was found that nearly half of all Maltese children aged between 11 and 12 years were overweight or obese. Also in another study on a sample of Maltese children aged between 10 and 11 years, Decelis et al. (2014) found that during weekdays 44% of Maltese boys and 28% of the girls spent more than one hour on computer or electronic games, whereas during the weekend 51% of the boys and 35% of the girls spent more than one hour on computer and electronic games. In this later study they also found that 20% of both boys and girls were overweight and 14% were obese.

Durnin (1989) has shown that physical activity or the lack of it, affects the mental and physical development almost from the age at which the infant begins to crawl. A study in 34 European countries by Jannsen et al. (2004) confirmed that Maltese children ranked high in the list of obese children. Sedentary behaviours which included watching T.V. and using electronic media and computers were strongly correlated with being overweight, and this finding was consistent throughout the 34 countries. This was a significant observation considering the different backgrounds and different population groups of these countries. Only 25.6% of the Maltese children surveyed were physically active. This was one of the lowest figures among the surveyed countries. On the other hand, 42.7% of them reported watching T.V. for three or more hours during the weekday.

OBESITY AND LACK OF PHYSICAL ACTIVITY

The causes of overweight and obesity in children are complex. Decrease in physical activity and increased time spent in sedentary pursuits such as television viewing and other electronic media use are considered major contributors (Granich et al., 2008). During the increasing levels of sedentary behaviour there is reduced energy expenditure while energy intake remains unaltered. This will lead to a rising prevalence of overweight and obesity in children. Watching T.V. for more than 2 hours per day during childhood and adolescence has been shown to attribute to 17% of adult overweight (Hancox et al., 2004). T.V. viewing may contribute to overweight and obesity due to increased eating of snacks while watching T.V. (Van den Bulck and Van Mierlo, 2004) and also an increased demand for energy-dense foods advertised on T.V. (Halford et al., 2004). Another study by Salmon et al. (2006) showed that children who watch more than 2 hours of T.V. per day consume less fruit and vegetables and more high energy drinks. Also, it has also been shown by Veitch et al., (2006) that the time spent using electronic media may displace other activities that require more energy such as children's active free play.

CHILDHOOD OBESITY AS A HEALTH RISK

Obesity is now considered to be the most common nutrition-related disease of children in the developed world (Etelson et al., 2012). Childhood obesity can also be a paediatric cardiovascular risk factor. Pardee et al. (2007) found that obese children and adolescents had an increased risk of hypertension related to higher levels of T.V. viewing. Overweight and obesity in children have been shown by Power et al. (1997) to be significantly associated with long-term morbidity and mortality. The most important long-term consequence of childhood obesity is persistence into adulthood. Furthermore, according to Freedman et al. (2001) there is also a relationship between childhood overweight and coronary heart disease risk factors in adulthood. Obese children typically continue to have a weight problem through adulthood (Laessle et al., 2001), when they risk the well-known comorbidities of adult obesity (Must, et al., 1999). A study by Lobstein et al. (2004) showed that childhood obesity will lead to early heart and circulatory diseases.

One particular study did not confirm this correlation of childhood obesity with adult health risk. According to Wright et al. (2001) only children who were obese at 13 showed an increased risk of obesity as adults. They also found that no excess adult health risk from childhood or teenage overweight was found and being thin in childhood offered no protection against adult obesity. Therefore, the long term importance of obesity in childhood is not entirely clear.

According to Etelson et al. (2012) parents of overweight children systematically underestimate their children's weight, and even parents who realize that they have an obese child and recognize this condition as a health risk may not know that obese children are more likely to become obese adults. Parents need to be involved in obesity prevention programmes and for such programmes to be successful, however, pediatricians and other health care professionals must facilitate parental awareness of obesity.

SEDENTARY BEHAVIOURS AND HEALTH EFFECTS

There is evidence that indicates that various markers of sedentary behaviour, including T.V. viewing and sitting down, are deleteriously related with chronic disease morbidity and mortality (Atkin et al., 2012). If the causality is established, the risk associated with negative effects on the health of the population of sedentary behaviours is potentially big as these behaviours are widespread among children. Excessive T.V. viewing and other sedentary behaviours have been linked to other negative outcomes among children such as poor cognitive performance, anti-social behaviour and reduced sleep time (Dworak et al., 2007). A study by Hamer et al. (2009) showed that more time spent in front of television and screen entertainment time combined with low physical activity levels interact to increase psychological distress in young children aged 4 to 12 years.

Findings from a systemic review by Thorp et al. (2011) of studies done between 1996 and 2011 indicate a consistent relationship of self-reported sedentary behavior with mortality and with weight gain from childhood to the adult years. However, findings were mixed for associations with disease incidence, weight gain during adulthood, and cardiometabolic risk. This systemic review showed also that there is a growing body of evidence that sedentary behavior may be a distinct risk factor, independent of physical activity, for multiple adverse health outcomes in adults. This study concluded that other prospective studies using device-based measures are required to provide a clearer understanding of the impact of sedentary time on health outcomes.

SEDENTARY BEHAVIOUR AND GENDER

According to Biddle (2007), boys in Australia watch more T.V. than girls but show less obesity and greater physical activity. A study in active Brazilian adolescents showed that physical activity level was associated with body composition (body weight, fat mass and fat-free mass) after adjustment for age and maturation, with differences between genders (Nogueira et al. 2009).

In a cross-sectional study by te Velde et al. (2007) on the patterns in sedentary behaviours and associations with overweight in 9 - 14 year-old boys and girls in nine countries, it was shown that boys spent more time on sedentary behaviours but also more on physical exercise than girls. High T.V. viewing and low exercise behaviour independently increased the risk of being overweight. This study also showed that among boys, there was a clear association between being overweight and the most unhealthy behaviour pattern having the highest risks of being overweight. It was also shown that girls who viewed T.V. and used the computer for long hours had an increased risk of being overweight. In girls, sedentary behaviours seemed more important than physical exercise with regard to overweight status. Also, according to this study, the differences between boys and girls regarding the behaviours and risks for overweight were noteworthy. A local study among year 5 pupils (aged 9 to 10 years) showed that boys were much more physically active than girls (Micallef, 2006).

In a cohort study among Gozitan Primary School students attending Year 5 (aged 9 to 10 years) it was found that there was a significant difference between the body mass index (BMI) of girls and boys ($p=0.003$); the BMI of girls was slightly lower than that of boys (Saliba, 2011). Twenty two per cent of the boys and 15.9% of the girls were overweight, while 29% of the boys and 11.7% of the girls were obese. In a study among Maltese students aged 11 and 12 years, Decelis et al. (2014) found that girls were less active than the boys meaning that the boys ran about or did some form of physical activity more than the girls. In their study they also found that 16% of the girls were overweight and 15% were obese, whereas of the boys 24% were overweight and 13% were obese.

FAMILY AND HOME ENVIRONMENT AND SEDENTARY BEHAVIOUR

Having a media-rich physical home environment is commonplace nowadays. There are also many households who keep such equipment in children's rooms and bedrooms thus increasing the possibility of T.V. viewing and game playing. All these provide an enticing setting for electronic media use among children. Children who have older siblings who spend considerable amounts of time playing electronic or computer games were more likely to do the same (Taylor et al., 1994).

The broader family environment has also been shown to be influential with factors such as family T.V. viewing habits (Saelens et al., 2002), T.V. viewing rules, eating meals while watching T.V. and family structure and family dynamics (Granich et al., 2008) related to T.V. and other electronic media use. In a local study among Form 3 male students, a correlation was found between computer and videogame occurrence in the bedroom and hours of individual media use, as opposed to no correlation for T.V. (Mercieca, 2010). This may be due to the decrease in the use of T.V and the increase in the use of computer, tablets, smart phones and electronic media. These gadgets can be easily taken into the bedroom and parents are having less control over the use of these electronic tools.

OTHER FACTORS AFFECTING PHYSICAL ACTIVITY

Computers, social media and electronic games are playing a very important role in the daily lives of our children. Compared to other children, Maltese children are spending more than 3 hours watching T.V. or using electronic media per day during the weekends (Saliba, 2011). This is higher than the average 2 hours which are recommended by Australian guidelines (Biddle, 2007) and American Academy of Paediatrics guidelines (2001). A type of sedentary behaviour which was only measured in the Gozo study (Saliba, 2011) was the amount of time spent by children attending church and lessons by the Society of Christian Doctrine (M.U.S.E.U.M.). This was 33 minutes per day during the week. This amount of time could affect negatively the amount of time spent in physical activity. Another sedentary activity measured in Gozitan students which could affect the time of physical activity was the amount of time spent attending private lessons outside school hours. Thirty-three per cent of students in government schools and 12% of students attending church schools spend one hour per week attending private lessons.

According to Saliba (2011), 15% of the Gozitan students did not read for leisure during the weekend, and only 21.9% of the students read for 2 hours or more during the weekend. This was surprising considering that during the weekend they were supposed to have more free time at their disposal. Reading did not seem to be a popular hobby amongst this age-group. If one

were to add the average time spent in reading to the amount spent on homework, including homework using the computer, this will add up to a total of 2 and a half hours (150 minutes) which is quite a considerable time. Adding 6 hours of school time to this, one would obtain a total of about 8 hours 50 minutes of school and school-related work.

SPECIFIC INTERVENTIONS TO REDUCE SEDENTARY BEHAVIOUR

The American Academy of Paediatrics (2001) recommends a number of guidelines for parents regarding television use by children. These include limitation of children's total media time to no more than 1 or 2 hours of quality programming per day, removal of electronic media gadgets from children's bedrooms, discourage television viewing for children younger than 2 years, monitoring of things children are doing with electronic gadgets, viewing of programmes along with children and discussing the contents, and encouraging alternative entertainment for children, including reading, athletics, hobbies and creative play.

The Walking Bus Project (Decelis et al., 2009) can be an excellent idea to increase physical activity among school children and at the same time leading to a cleaner environment. Children meet every morning at the bus terminus or bus stops and walk to school as a group accompanied by a parent. One of the parents collects the school bags and carries them in a car. On arrival at school, children collect their respective bags and walk in. Children who participate in the project are allowed free use of a sports complex which apart from being a sort of a reward encourages more physical activity.

Finally Carter (2006) claimed that interventions aimed at reducing childhood obesity by tackling television viewing and playing computer games were unlikely to have much effect at all, and therefore parents and not T.V. or electronic screens should be targeted. More control by parents is needed so that children will make better use of these useful modern tools.

CONCLUSIONS

Lack of physical activity or sedentary behaviour can lead to a number of negative effects on the well-being of children and this may later on affect their health in early adulthood. There is a correlation between the lack of physical activity or sedentary behaviour and childhood obesity.

Gender differences need to be considered when developing tailored intervention strategies for prevention of overweight. On the other hand, public health awareness directed to enhance physical activity and decrease sedentary lifestyle among youngsters should focus equally to urban and rural children.

Parents and the school need to be involved in obesity prevention programmes. The health authorities need to make public campaigns of awareness of obesity amongst children and the importance of healthy nutrition and physical activity. Healthcare workers including family doctors and paediatricians need to facilitate parental awareness of obesity.

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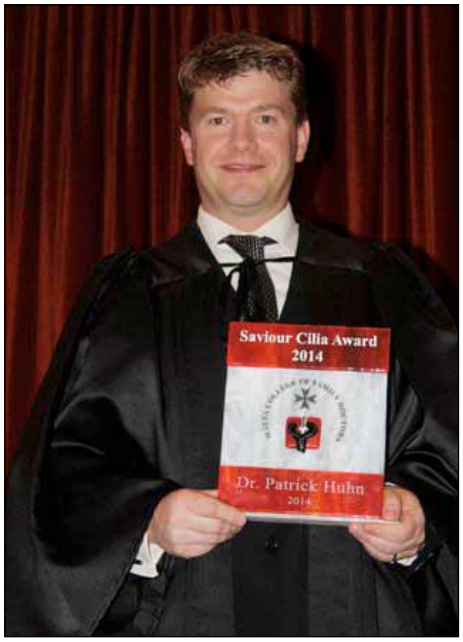
FMCFD conferment and MMCFD graduation at MCFD 25th Anniversary Dinner, Attard

27th October 2015



A study on the management of corticosteroid side effects in cancer patients

Dr Clayton John FSADNI

ABSTRACT

Background

Systemic corticosteroids lead to many adverse effects especially in cancer patients. Preventive measures and treatment options are essential to minimise such side effects.

Objectives

The aims of the study included the evaluation of the prescribers' management of corticosteroid induced hyperglycaemia, dyspepsia, oral candidiasis and proximal myopathy, the discussion of possible reasons for non-adherence to guidelines, and the recommendation of interventions to reduce their risk of occurrence.

Method

A retrospective review of the medical records for 156 consecutive patients at oncology out-patients and in oncology wards of Boffa Hospital between the 1st and the 14th September 2014 was performed. Only patients who were on long term corticosteroids (>2 weeks' duration) were considered. Patients younger than 12 years of age or those that were prescribed corticosteroids for antiemetic purposes were excluded from the study. For each of the sampled patients, any management aimed at reducing corticosteroid side effects was compared to the guidelines as stated in an article published in a prominent international journal.

Results

From 156 cancer patients, 55 patients satisfied the inclusion criteria. The mostly addressed side effect was dyspepsia (n=35; 63.6%) followed by proximal myopathy (n=27; 49%), hyperglycaemia (n=24; 43.6%) and lastly oral candidiasis (n=20; 36%). Adherence to guidelines was as follows: hyperglycaemia – haemo-glucose test (HGT) and glycated haemoglobin (HbA1c) (36%); dyspepsia - prescribing of omeprazole (51%) and ranitidine (5%); oral candidiasis - orophargyngeal exam (29%); and proximal myopathy (40% compliance; of which 35% complying with resistance and endurance exercise and 5% complying with steroid dose reduction).

Conclusion

Improvement is required with regards to the management of corticosteroid side effects especially for hyperglycaemia and oral candidiasis. Possible actions that may be taken include strategies to improve guideline awareness, the prescribing of the lowest effective dose, adequate patient education and the implementation of a steroid card.

KEYWORDS

Disease management; adrenal cortex hormones; drug-related side effects and adverse reactions; neoplasms; humans

INTRODUCTION

Corticosteroids have many indications for use in palliative care and oncology, primarily owing to their anti-inflammatory properties (Lussier *et al.,* 2004).

Despite their beneficial effects, long term systemic (oral or parenteral) use of these agents is associated with well known adverse events mainly hyperglycaemia, dyspepsia, oral candidiasis and proximal myopathy.

It is therefore the role of the clinician to minimize the risk of such side effects through appropriate active and proactive management, especially in debilitating patients such as cancer patients.

The main aims of the study include:

- To evaluate the prescribers' management of corticosteroid side effects, specifically for hyperglycaemia, dyspepsia, oral candidiasis and proximal myopathy;
- To discuss possible reasons for non-adherence to guidelines; and
- To recommend possible interventions to reduce their risk of occurrence.

All this should make the prescriber more aware of corticosteroid side effects in cancer patients as well as providing him with a variety of options for optimally addressing or preventing the manifestation of adverse effects.

For a better understanding of the study, the term "management" will be used to refer to either or both *clinical management* and *pro-active approach*. On the other hand "addressing" a side effect will include one or all of clinical assessment, clinical education, and treatment.

METHOD

Setting and sampling units

The study was conducted between the 1st and the 14th of September 2014 as a retrospective analysis of case notes. Medical notes and treatment regimes for 156 patients were reviewed from Oncology and Palliative Care Outpatients, Day Ward, Oncology Wards and the Palliative Care Unit.

Selection criteria

Inclusion criteria included adult oncology and palliative care patients who were prescribed, or had the intention of being prescribed dexamethasone or prednisolone for more than 2 weeks. Hyperglycaemia, dyspepsia, oral candidiasis and proximal myopathy were assessed due to their high prevalence in cancer patients, ease of management and monitoring.

The exclusion criteria included corticosteroids prescribed for short term intervals as adjuvant antiemetic with chemotherapy. Patients younger than 12 years of age were not included in the study.

When considering such selection criteria, from the 156 case notes that were reviewed only 55 qualified for the study, and hence had their case notes evaluated.

Measuring performance

Performance was measured from the time the patient was first prescribed steroids for a 2-week treatment duration or more.

Performance was measured in terms of:

(1) Clinical assessment for side effect detection,
(2) Clinical education to patient, and
(3) Clinical action in addressing the already manifested side effect

There are no locally established guidelines and hence the guidelines that were used were those stated in a paper entitled "A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy" in the Allergy, Asthma and Clinical Immunology Journal (Liu *et al.*, 2013).

A proforma sheet was produced for each of the side effects previously mentioned and filled in for every patient. Data was processed using Microsoft Excel 2013.

The performance was measured by comparing the management stated in the notes with that of the guidelines. Compliance was calculated as follows: the number of patients on whom an intervention was performed as per guidelines, ***divided by*** the total number of patients sampled (n=55) ***multiplied by*** 100%

Pilot study (10%)

A pilot study was undertaken 2 days prior to the 2-week data retrieval period. Twenty case notes were reviewed of which 6 could be evaluated as they satisfied the selection criteria. The proforma for the 6 patients was effective in measuring performance without major bias. Hence no changes to the original proforma were made other than extending the retrieval time period from two days to a fourteen day time window.

Ethical approval and consent

The study was approved by the Audit and the Data Protection Act committees. Consent was achieved from the Chairman of Oncology/Haematology and all oncologists at Sir Paul Boffa Hospital. The University Research and Ethics Committee was not involved as no human subjects were involved – only case notes were utilised for data retrieval.

RESULTS

Corticosteroids were prescribed in 12 known primaries (n=54; 98%). Figure 1 shows the number of patients for each of the primary carcinomas to which a long term corticosteroid was prescribed. The main indications were for nerve pain, control in bone metastases and other metastases mainly of the lung and the liver. With regard to brain primaries, namely astrocytoma and glioblastoma, steroids were indicated due to the direct effect of the tumour on the intracranial pressure (n=5; 9%). Other

indications included decreased appetite (n=6; 11%) and emesis (n=2; 3.7%).

Dexamethasone and prednisolone were the only corticosteroids to be prescribed. Seventy-five per cent (n=41) of all patients were prescribed the former, with the 2mg daily dose being the most prescribed regimen (n=14; 34%). Figures 2a and 2b represent the corticosteroid doses. Treatment duration spanned from 2 weeks to 3 and a half years (Figure 3), with 1 month being the most common treatment duration (n=20; 36%).

Table 1 indicated that the most addressed side effect was dyspepsia (n=35; 64%), followed by proximal myopathy (n=27; 49%), hyperglycaemia (n=24; 44%) and lastly oral candidiasis (n=20; 36%).

Although, for convenience sake, the management of each side effect was classified into clinical assessment, education and action (treatment) it is to be noted that the three interventions could all have been done individually or combined together in the same patient.

Management of hyperglycaemia

Hyperglycaemia was addressed in less than half of the patients (n=24; 44%). Such patients were managed as shown in Figure 4, where monotherapy was the mainstay of treatment. Haemo gluco testing (HGT) was the most common method used to address hyperglycaemia proactively (n=19; 35%).

Management of dyspepsia

Only a pro-active approach was implemented, mainly in the form of gastroprotective agents, of which omeprazole (n=28; 51 %) was preferred over ranitidine (n=3; 9%) and their combination (n=4; 11%) (Figure 5).

Management of oral candidiasis

Oral candidiasis was mainly addressed pro-actively whereby oropharyngeal examination was the most common method (n=16; 29%) to be employed (Figure 6).

Management of proximal myopathy

Both clinical management and a proactive approach were given similar importance. As shown in Figure 7, assessment of lower limb power (n=21; 38%) and physiotherapy referral for quadriceps strengthening (n=19; 35%) were the commonest strategies employed.

Tables 2a and 2b provide a summarised comparative study, including percentage compliance, for each side effect.

DISCUSSION

The importance of long term steroid use in cancer patients

Corticosteroids are commonly used in the treatment of cancer, primarily owing to their anti-inflammatory activities (Rhen and Cidlowski, 2005). Recently it has been found that corticosteroids may have a direct effect on the modulation of tumour biology and angiogenesis as well as on tumour-associated pain (Dietrich *et al.,* 2011). Other benefits include limiting nausea and vomiting and improving appetite in cancer patients.

Side effects related to long term steroid use

In a prospective study the most common side effects associated with corticosteroid use (at 10–30 mg/day of prednisolone and 4-16mg/day of dexamethasone) were oral candidiasis (26% with prednisolone, 37% with dexamethasone), oedema (18% prednisolone, 21% dexamethasone), cushingoid facies (15% prednisolone, 21% dexamethasone), dyspepsia (8% prednisolone, 9% dexamethasone), and weight gain (4% prednisolone, 5% dexamethasone) (Dorffl and Crawford, 2013). A separate study states that hyperglycaemia occurs in a majority of hospitalised patients receiving high doses of corticosteroids (Donihi *et al.,* 2006). Table 3 provides a summary of adverse effects associated with corticosteroid dose.

Table 1: Percentage of patients managed for corticosteroid side effects

Side Effect	Management (%) (n=55)	No management (%) (n=55)
Hyperglycaemia	44	56
Dyspepsia	64	36
Oral Candidiasis	36	64
Proximal Myopathy	49	51

Table 2a: Percentage compliance with management guidelines for hyperglycaemia

Guidelines	Study	Compliance
Proactive Approach • Education about the classic signs and symptoms of hyperglycemia. • Monitoring of glycated haemoglobin, fasting plasma glucose, 2hr plasma glucose using a 75-g oral glucose tolerance test. • Blood glucose should be monitored within 8 hours of the first dose. And then at least 48 hrs after initiation of corticosteroid therapy, regardless of whether or not the patient is diabetic.	**Proactive Approach** • Haemo glucose and glycated haemoglobin testing.	36%
Clinical Management • Management guidelines as in those with pre-established diabetes. If <15mmol/L- metformin, sulphonureas, meglitinides or GLP-1 agonists. Sulphonureas (single dose) for prednisolone regimens and glicliazide MR or glimepride for dexamethasone as this is longer acting. If >15mmol/l insulin and metformin is recommended • Steroid dose reduction leads to improvement • Discontinuation usually leads to complete reversal	**Clinical Management** • Dietary advice • Metformin • Insulatard • Actrapid • Metformin+Glicliazide +Actrapid	13%

Table 2b: Percentage compliance with management guidelines for dyspepsia, oral candidiasis and proximal myopathy

Side effect	Guidelines	Study	Compliance
Dyspepsia	**Proactive Approach** • Use of proton pump inhibitors for gastrointestinal protection in corticosteroid users at high risk of gastrointestinal bleeding or peptic ulcers for example those on non-steroidal anti-inflammatory drugs, cancer patients, history of ulcers or gastrointestinal bleeding, and those with serious comorbidities (i.e., advanced cancer)	**Proactive Approach** • Use of omeprazole, ranitidine or their combination	51%
Oral Condidiasis	**Proactive Approach** • Early recognition of infections through oropharyngeal examination	**Proactive Approach** • Early recognition of infections through oropharyngeal examination • History taking • Regular mouth hygiene **Clinical management** • Miconazole or nysatin with or without the use of mouthwash	29%
Proximal Myopathy	**Clinical Management** • Reduction or discontinuation of steroid use as soon as possible. • Resistance and endurance exercise	**Proactive Approach** • Assessment of lower limb power and advice on the possibility of muscle weakness **Clinical management** • Physiotherapy referral and quadriceps strengthening	40%

Table 3: Adverse effects associated with steroid dosage regimen (Hanks et al., 1983)

Adverse Effect	Corticosteroid type and dose for adverse effects
Hyperglycemia	Low-dose dexamethasone (0.5-2 mg/day)
Infection	Low-dose predmisone (10 mg/day)
Myopathy	Low-dose predmisone (10 mg/day)
Osteoporosis	Low-dose predmisone (10 mg/day)
Oedema	Low-dose predmisone (10 mg/day)
Weight gain	Low-dose predmisone (10 mg/day)
Dyspnoea	Low-dose predmisone (10 mg/day)
Cushingoid facies	Low-dose dexamethasone (0.5-2 mg/day)

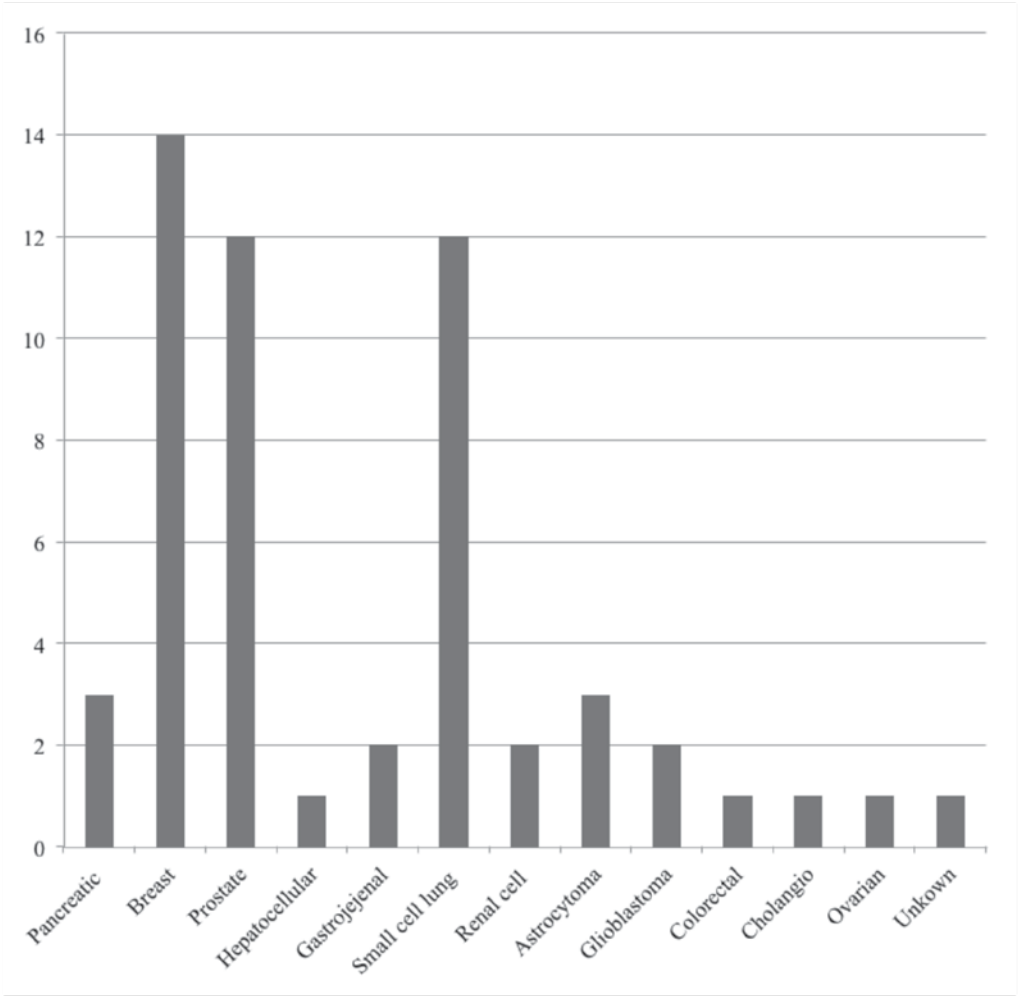


Figure 1: Number of patients (n=55) that were prescribed long term corticosteroids for each of the diagnosed primary carcinomas

Figure 2a: Number of patients (n=41) that were prescribed dexamethasone by different doses

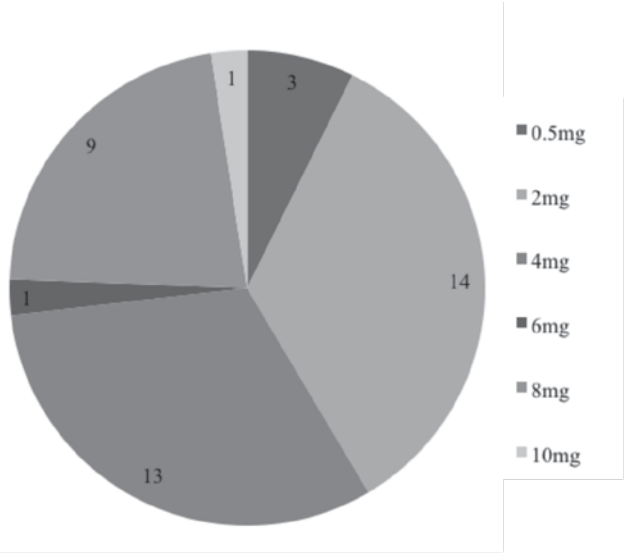


Figure 2b: Number of patients (n=14) that were prescribed prednisolone by different doses

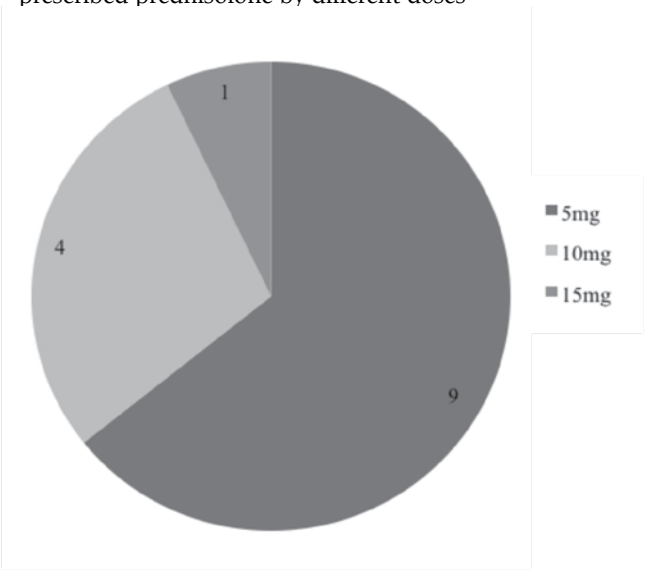
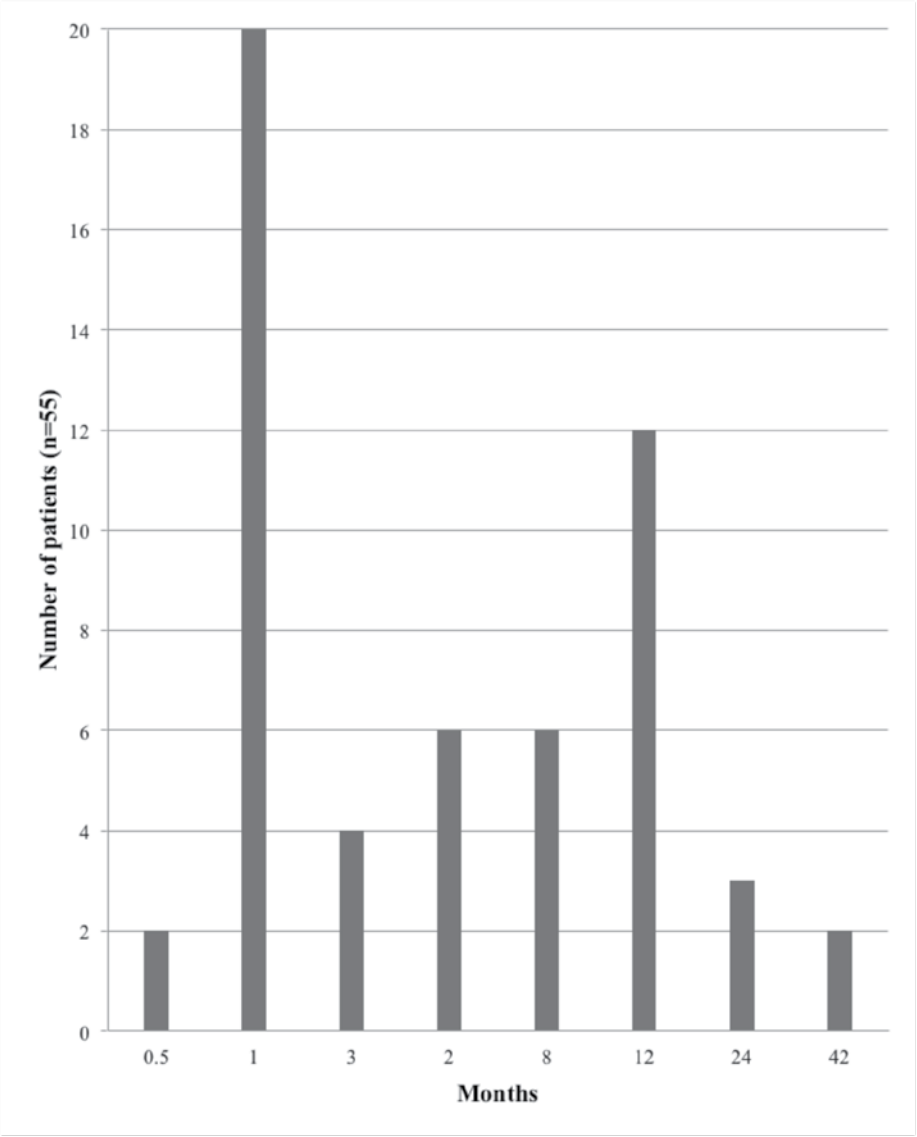


Figure 3: Treatment duration (months) of corticosteroid therapy (n=55)



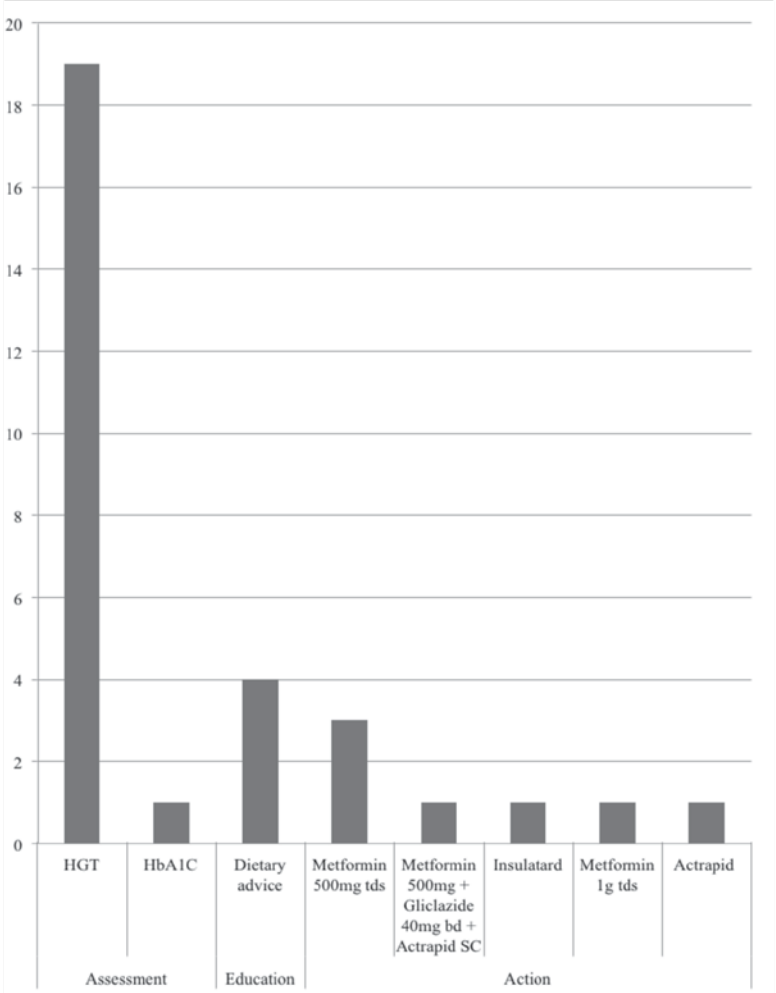


Figure 4: Management of hyperglycaemia (n=55)

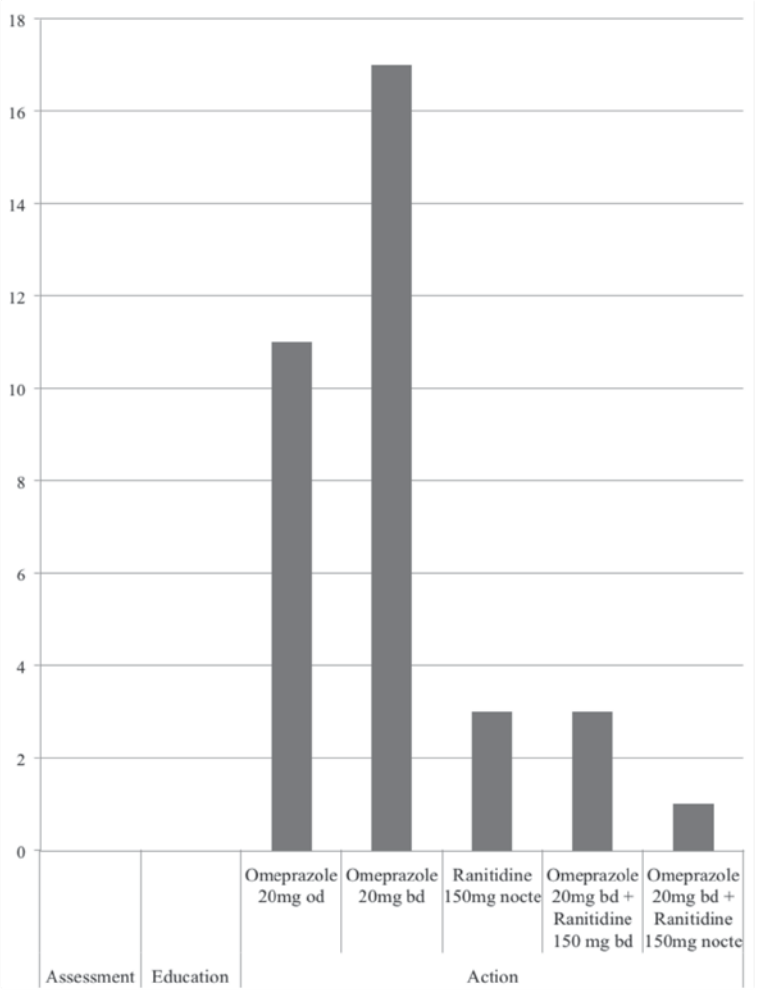


Figure 5: Management of dyspepsia (n=55)

Figure 6: Management of oral candidiasis (n=55)

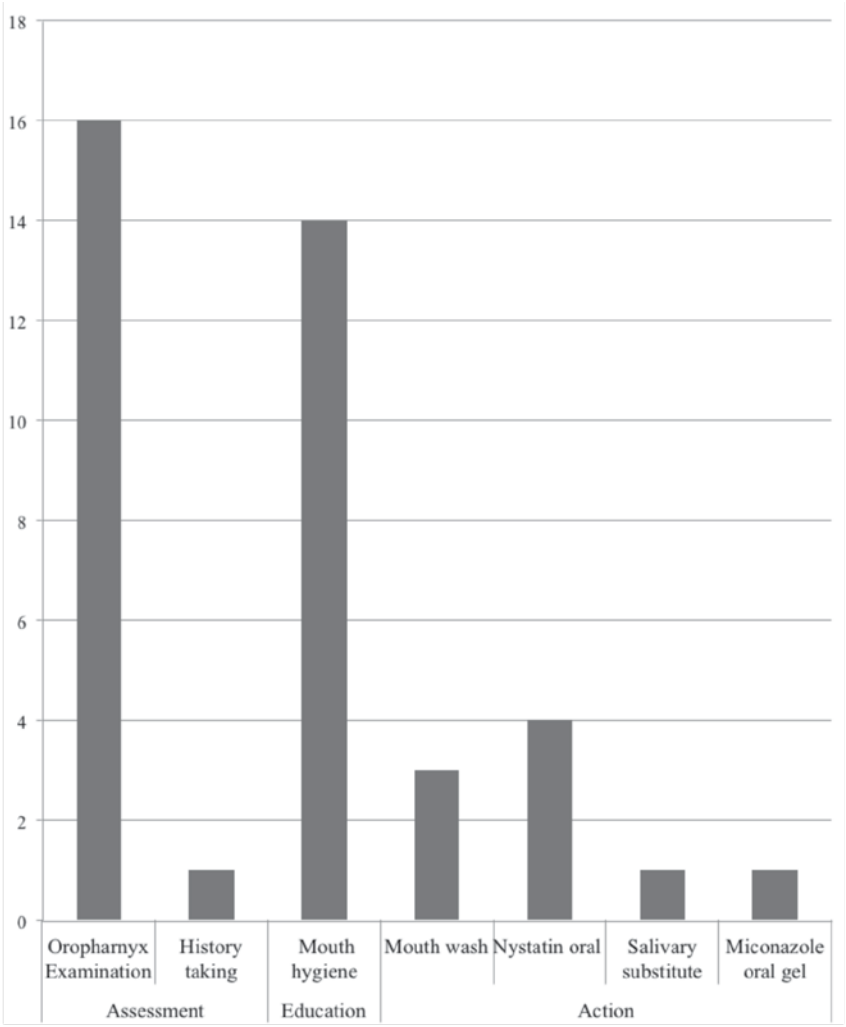
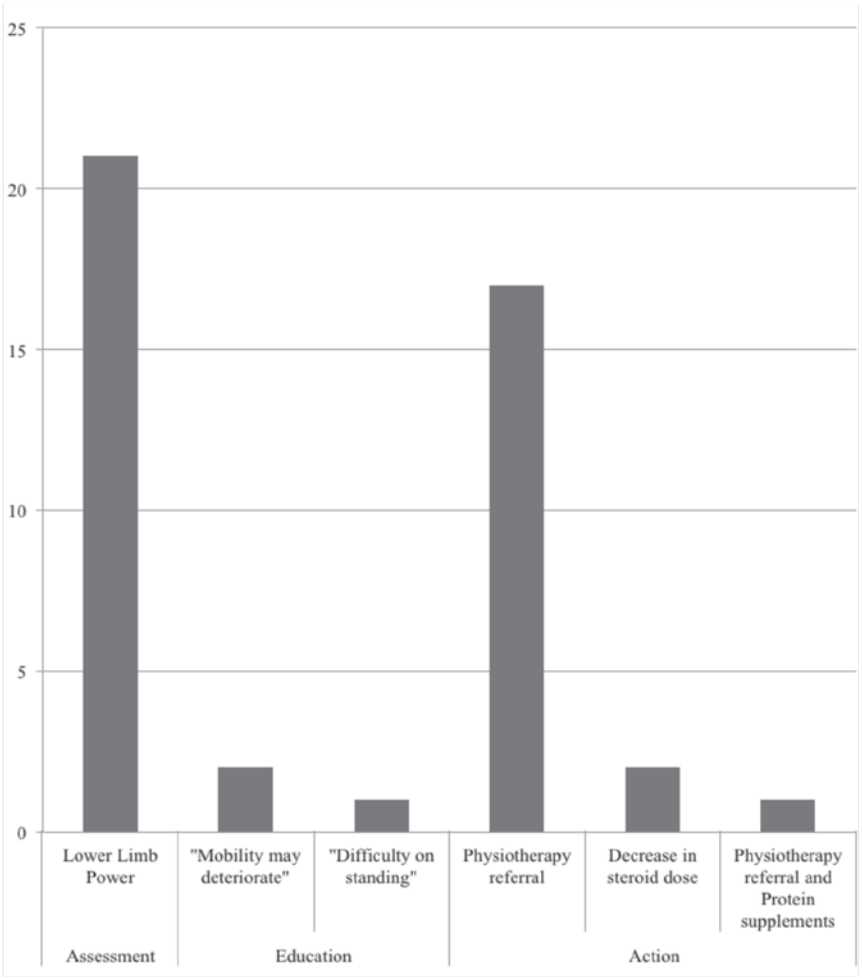


Figure 7: Management of Proximal Myopathy (n=55)



As described previously the indications of corticosteroid therapy require relatively potent corticosteroids with long term and high dose regimens. In this study the mostly prescribed steroid was dexamethasone (75%) at a dosage regimen of 2mg daily (34%) for 1 month (36%).

1. Hyperglycaemia

Glucocorticoids decrease glucose utilisation and increase hepatic glucose production, leading to hyperglycaemia; nonetheless the development of frank diabetes in a previously normal patient is uncommon (Moghadam-Kia and Werth, 2010). The effects of glucocorticoid administration on glucose levels are observed within hours of steroid exposure and appear to be dose dependent (Liu *et al,* 2013).

From the results of this study, less than half of the patients on long term steroids (43.6%) were managed for hyperglycaemia in any way. One reason for this might be that most of the steroid doses were not high enough to cause any concern among physicians. A less likely reason might also be that there was lack of awareness or lack of documentation among physicians.

Comparing to guidelines: proactive approach

Thirty-six per cent of patients were proactively managed according to guidelines only through HGT and HbA1c monitoring. No mention was made of whether the blood glucose levels were pre or post dose. Nonetheless there was no mention of any educational advice given with regards to the classic signs of hyperglycaemia. It is to be noted that educational advice could have been mentioned but not documented.

Comparing to guidelines: clinical management

Glycaemic targets for patients with corticosteroid-induced diabetes should be individualised, but for most patients, fasting plasma glucose and 2-hour plasma glucose targets of 4.0-7.0 mmol/L and 5–10 mmol/L respectively, are recommended (Cheng *et al,* 2013).

Thirteen per cent of patients were actively managed according to guidelines but compliance of this was only partial as insulin and metformin were given only to patients who had pre-existing diabetes and not specifically to those with steroid induced diabetes of levels >15mmol/L. Thus oral hypoglycaemics, as monotherapy, were the mainstay of treatment in this case. Such management would have been improved if a referral to a multidisciplinary diabetes team was conducted (Liu *et al,* 2013).

None of the clinicians resorted to a decrease in steroid dose or discontinuation of treatment as suggested by the guidelines. This may have been due to the fact that the benefit of steroid use at a therapeutic level outweighed the risks of hyperglycaemia.

It can be said that more is desired with respect to proactive management as the tests done are minimally invasive, non time-consuming and reliable. From the clinicians' point of view, awareness of glucose level cut-off points and steroid pharmacokinetics is paramount for optimal pharmacological glucose control. Patients should always be made aware of the most common clinical signs of hyperglycaemia so that help is sought immediately as this would allow prompt action to be employed.

2. Dyspepisa

The use of systemic glucocorticoids is associated with gastrointestinal (GI) side effects including gastritis, peptic ulceration and gastrointestinal haemorrhage (Moghadam-Kia and Werth, 2010). Recent evidence suggests that the risk of peptic ulcer disease due to corticosteroid alone is low, but increases significantly when these agents are used in combination with non-steroidal anti-inflammatory drugs (NSAIDs) (Hawkey & Longman, 2003).

In this study, dyspepsia was found to be the side effect which physicians were mostly aware of. It was found that protection was mostly offered to those patients with a high risk of GI bleeding or peptic ulcers. As stated by Hawkey & Longman (2003), corticosteroids act only as an NSAID specific risk magnifier and hence this may give rise to the debate of whether corticosteroids on their own increase risk of gastritis. This lack of clarity in evidence-based material might explain the rationale why a gastro-protective agent was not commonly prescribed in patients that have no history of gastritis, ulceration or GI bleeding.

Comparing to guidelines: proactive approach

As per the guidelines, management was only in the proactive form, with omeprazole being the most commonly prescribed. When compared to H_2 receptor antagonists, the proton pump inhibitors are a superior treatment modality for ulcer healing due to their ability to effectively control acid (Meijia and Kraft, 2009). No evidence based rationale was found that state that ranitidine and omeprazole combination therapy is more effective than omeprazole on its own.

Physicians may also have opted more for omeprazole since its dosage form is in capsule form and hence easier to swallow than ranitidine. Another reason for prescribing omeprazole could

have the physicians' awareness of the recommended prophylactic use of 20mg omeprazole in steroid induced ulcers (Lanza *et al,* 2009).

It is to be noted that patient advice with regards to lifestyle and steroid administration was not performed or not documented.

3. Oral candidiasis

Corticosteroids have been shown to affect T-cells by inducing thymocyte apoptosis after polyclonal T-cell activation, leading to reduced function of the immune system (Herold, McPherson and Reichardt, 2006).

Owing to the immunosuppressive effects of corticosteroids, patients may be at increased risk for increased risk of topical bacterial and fungal infections (Systemic steroids, 2014).

Hence it can be said that prednisolone and dexamethasone doses of more than 10mg and 1.5mg respectively can lead to a significant risk of oral candidiasis (Poetker and Reh, 2010).

The study shows that only 36% of patients on long term steroids where addressed for potential oral candidiasis, making it the least managed steroid induced side effect. Seventy-one per cent of patients of the same cohort were taking prednisolone or dexamethasone doses that were greater than 10mg and 0.5mg respectively and hence would have warranted a form of management (see Table 3). Reasons for this could be either failure of documentation or lack of clinicians' awareness.

Comparing to guidelines: proactive approach

Compliance to guidelines was achieved in 29% of patients of whom an orophargyngeal exam was conducted prior to commencement of corticosteroid therapy. Reasons for physicians not performing an oropharyngeal examination may be lack of awareness or failure to document. Oral candidiasis is mainly diagnosed clinically and hence awareness among physicians to look for clinical signs during follow up or before increasing corticosteroid dose is essential. Other proactive management actions that were performed by the physicians but not mentioned in guidelines included mouth hygiene and further history taking.

Comparing to guidelines: clinical management

The guidelines do not specify any form of active management but the study indicated that 16 % of patients were prescribed either a mouth wash or a form of a topical antifungal. This lack of compliance may be due to the fact that the guidelines were not formulated specifically for cancer patients. As in this case, active management may be appropriate in immunosuppressants secondary to carcinomas (Liu *et al.,* 2013), but routine primary prophylaxis is not recommended. However, if recurrences are frequent or severe, oral fluconazole can be used for either oropharyngeal or vulvovaginal candidiasis (Kaplan *et al.,* 2009).

Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including nystatin suspension or miconazole oral gel. Routine general advice about maintaining oral hygiene is always appropriate at any steroid regimen prescribed.

4. Proximal myopathy

Glucocorticoids have a direct catabolic effect on skeletal muscle (Sun *et al.,* 2008). Onset of symptoms usually takes several weeks, and patients typically present with proximal muscle weakness and atrophy in both the upper and lower extremities (Moghadam-Kia and Werth, 2010).

It was found that half of the patients on long term steroids were managed for proximal myopathy. Lower limb power assessment, physiotherapy referrals and quadriceps strengthening were the most common forms of management respectively. Patient education was observed only in 5% of patients most probably because of failure in documentation. It is vital to clarify to the patient the fact that weakness is due to corticosteroid effect rather than due to cancer progression.

In those patients that were not managed, prednisolone doses were less than 10mg and the likelihood of side effect manifestation is very low. But 43 % of such patients were on average daily dexamethasone doses greater than 1.5mg (equivalent to 10mg prednisolone) - see Table 3. This means there may be lack of knowledge with regards to steroid dosing and proximal myopathy.

Comparing to guidelines

According to the guidelines only clinical management is to be considered. Compliance was mostly noted when it came to resistance and endurance exercises. Some literature suggests that aerobic exercises and resistance training may help to prevent weakness or reduce its severity (Foye, 2015).

A proactive approach, a low steroid dose, low potency or insufficient regimen duration for steroid-induced myopathy may have reduced steroid manifestation and hence in practice this might have led

to less manifestations and hence less clinical management. Other possibilities for non-adherence may be lack of awareness and failure to document.

The main treatment recommendations for steroid myopathy are a decrease in the dose of steroid to below a threshold level or the discontinuation of the corticosteroid's use. Alternate-day dosing could also be considered (Gupta and Gupta, 2013). But again reduction in steroid dose was an uncommon choice with physicians. Physicians may have opted out of this option as benefits of corticosteroid use may have outweighed the risks of proximal myopathy manifestation or worsening of the condition.

Limitations

Many limitations were encountered in the study. Firstly, the guidelines to which the results were compared were not specifically formulated for cancer patients but for patients with inflammatory and immunological conditions that required long term systemic corticosteroid use. Due to time constraints only the most common clinically encountered side effects were considered. Osteoporosis, skin atrophy and psychiatric side effects were not assessed. Furthermore, although differences in monitoring and care exist between adults and children, only the adult population was sampled.

With regards to data collection, this was based only on what the clinicians had documented, and hence may not reliably reflect the actual intention of the prescriber. For example advice may have been given by the clinician but not necessarily documented.

Although the cancer type, steroid doses and duration of treatment were recorded, in view of time constraints, the effect of such steroid regimens on the manifestation of type and severity of side effect were not evaluated. It was also assumed that the side effects were purely long-term corticosteroid induced and not affected by other causes, e.g. comorbidities (cancer), drug interaction, etc.

Recommendations

This study has shown that hyperglycaemia, oral candidiasis, heartburn and proximal myopathy may often be overlooked in cancer patients who are on long-term steroids. If proactive and / or active management is to be provided, it is vital that patient assessment, education and appropriate treatment is sought.

From the study several recommendations can be highlighted that would help to improve the management of steroid side effects. Firstly, awareness amongst physicians of the above-mentioned guidelines is essential if they are to be followed and applied accordingly. These should be clear, regularly updated, well disseminated and enforced. One practical way to ensure this would be to make these management guidelines available on Mater Dei's Intranet (Kura) were they can be clear, easy to use regularly updated. Regular audits, the availability of hard copies on the wards and education campaigns are other ways by which awareness can be increased among prescribers.

Secondly, from the prescribers' side, documentation of any signs of corticosteroid side effects in medical notes is vital as their presence may affect the patient's management plan. This will also help when reviewing corticosteroid doses on weekly bases. Dexamethasone should be given as single morning dose, or if a higher dose needed give in 2 divided doses, the second being no later than 2 p.m. to minimise risk of sleep disturbance.

Thirdly, patients should be informed about the common corticosteroid side effects and advised on lifestyle modification strategies that may help reduce the risk of these events. If discharged home, the physician should instruct patients to seek medical advice in the case corticosteroid side effect manifestations (Princess Alice Hospice Guidelines for corticosteroid use in palliative care, 2008).

Patients on systemic steroids for >3 weeks must be given a steroid card so that it can be shown to all healthcare professionals involved in their care and management (North of England Cancer Network palliative care guidelines, 2013). This should include the indication for steroid use and the plan for dose reduction and monitoring. At end of life, if corticosteroids are prescribed for specific severe or serious symptom, these should be continued at the most convenient subcutaneous dose. If prescribed for 'general well-being' or appetite stimulation they should be discontinued.

The provision of educational leaflets may facilitate delivery of information to patients as well as save the clinician's time. Furthermore, the assistance of allied health care professionals in the clinical assessment and education prior to the patient's consultation with the physician may assist in the awareness of corticosteroid side effects.

CONCLUSION

Much has still to be done in order to implement management as proposed by guidelines for steroid induced side effects, especially when it comes to treatment

and prevention of steroid induced hyperglycaemia and oral candidiasis. These adverse effects are particularly important as they tend to be more severe and commoner in cancer patients than in the rest of the population.

Management should involve more careful patient monitoring and implementation of preventive measures, including the use of lower potency agents and the lowest effective dose required for management of the underlying condition. Management should also involve the treatment of the manifested side effects as well.

Furthermore, patients should be informed more about the side effects associated with systemic corticosteroid use and should be advised on lifestyle modification strategies that may help reduce the risk of these events. Patients should also be instructed to seek medical attention if they experience signs and symptoms of steroid-related side effects and should also be advised to carry a steroid treatment card that can be shown to all healthcare professionals involved in their care and management. Differences in the monitoring and care of adults versus children should also be noted.

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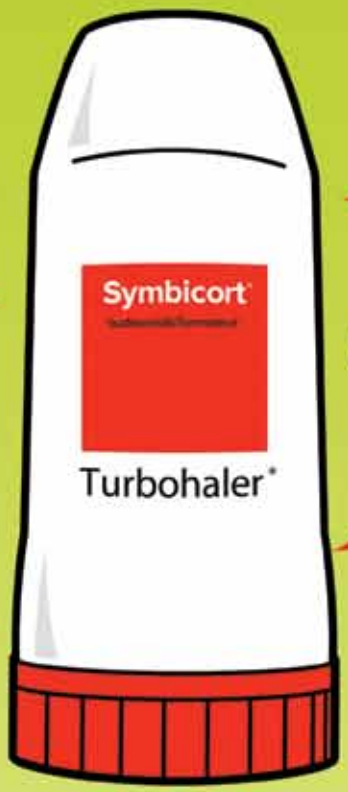

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Indication Asthma: Treatment of asthma where the use of a combination (inhaled corticosteroid and long acting β2 adrenoceptor agonist) is appropriate. Symbicort Turbohaler 100/6 is not appropriate for patients with severe asthma. **COPD *(Symbicort 200/6 only)*:** Symptomatic treatment of patients (with severe COPD (FEV1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.
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Dosage and Administration Asthma Not intended for the initial management of asthma. Dose should be individualised. If a patient requires dosages outside recommended regimen, appropriate doses using individual inhalers should be prescribed. When long-term symptoms are controlled, titrate to the lowest effective dose, which could include a once daily dosage. **Symbicort maintenance therapy – regular maintenance treatment with a separate rescue medication: *Adults (≥18 years, including elderly)*:** 1–2 inhalations twice daily (maximum 4 inhalations twice daily). ***Adolescents (12-17 years)*:** 1–2 inhalations twice daily. ***Children 6–11 years (Symbicort 100/6 only)*:** 2 inhalations twice daily. ***Children under 6 years*:** Not recommended.
Symbicort maintenance and reliever therapy – regular maintenance treatment and as needed in response to symptoms: consider for patients with (i) inadequate asthma control and in frequent need of reliever medication (ii) previous asthma exacerbations requiring medical intervention. ***Adults (including elderly)*:** 1 inhalation twice daily or as 2 inhalations once daily. 2 inhalations twice daily may be appropriate for some patients (200/6 strength only). Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is not normally needed; however, up to 12 inhalations a day could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice and should be reassessed; their maintenance therapy should be reconsidered. Patients should be advised to always have Symbicort for reliever use. ***Children and adolescents under 18 years of age*:** not recommended. **COPD *(Symbicort 200/6 only)*: *Adults (≥ 18 years)*:** 2 inhalations twice daily.
Contraindications Hypersensitivity to active substances or excipient.
Warnings and Precautions If treatment is ineffective, or exceeds the highest recommended dose therapy should be reassessed. Sudden and progressive deterioration in control requires urgent medical assessment. Treatment should not be stopped abruptly. Patients should have their appropriate rescue medication available at all times i.e. either Symbicort or a separate reliever. If needed before exercise a separate reliever should be used. Therapy should not be initiated during an exacerbation. Serious asthma-related adverse events and exacerbations may occur. If asthma symptoms remain uncontrolled or worsen patients should continue treatment but seek medical advice. If paradoxical bronchospasm occurs Symbicort should be discontinued. It responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Systemic effects may occur, particularly at high doses prescribed for long periods e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Height of children should be monitored. Potential effects on bone should be considered especially in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress e.g. severe infections or elective surgery. Transfer from oral steroid therapy to Symbicort may result in the appearance of allergic or arthritic symptoms which will need treatment. In rare cases, tiredness, headache, nausea and vomiting can occur due to insufficient glucocorticosteroid effect and temporary increase in the dose of oral glucocorticosteroids may be necessary. To minimise risk of oropharyngeal candida infection patients should rinse mouth with water. Observe caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, or severe cardiovascular disorders. Re-evaluate need for Symbicort in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways. Hypokalaemia may occur at high doses. Particular caution recommended in unstable or acute severe asthma. Monitor serum potassium levels. In diabetic patients consider additional blood glucose monitoring. The small amounts of milk proteins present may cause allergic reactions.
Drug Interactions Concomitant treatment with potent CYP3A4 inhibitors should be avoided. If this is not possible the time interval between administration should be as long as possible. Symbicort maintenance and reliever therapy is not recommended in these patients. Not recommended with beta adrenergic blockers (including eye-drops) unless compelling reasons. Concomitant administration with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine) and TCAs can prolong the QTc interval and increase the risk of ventricular arrhythmias. L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance. Concomitant administration with MAOIs, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertension. Elevated risk of arrhythmias in patients receiving anaesthesia with halogenated hydrocarbons. Hypokalaemia may increase the disposition towards arrhythmias in patients taking digitalis glycosides
Fertility, Pregnancy and Lactation No data available on the potential effect on fertility. During pregnancy: use only when the benefits outweigh the potential risks. Budesonide is excreted in breast milk, however at therapeutic doses no effects on the child are anticipated.
Undesirable effects Common: headache, palpitations, tremor, Candida infections in the oropharynx, coughing, mild irritation in the throat, hoarseness. Uncommon: tachycardia, muscle cramps, nausea, dizziness, bruises, aggression, psychomotor hyperactivity, anxiety, sleep disorders. Rare: hypokalaemia, cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles, bronchospasm and immediate and delayed hypersensitivity reactions including exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction. Very Rare: depression, behavioural changes (predominantly in children), angina pectoris, prolongation of QTc interval, hyperglycaemia, taste disturbance, Cushings syndrome, adrenal suppression, growth retardation, decrease in bone mineral density, cataract, glaucoma and variations in blood pressure. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases.
Package Quantities Each Symbicort Turbohaler contains 120 inhalations. **Legal Status** POM. **Marketing Authorisation Numbers** MA 046/00601-2. **Marketing Authorisation Holder (MAH)** AstraZeneca AB, Gartunavagen, S-151 85 Sodertalje, Sweden. **Further product information available on request from** Associated Drug Company Limited, Triq l-Esportaturi, Mriehel, Birkirkara BKR 3000, Malta. Tel: (+356) 2277 8118.
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Date of preparation: April 2015

Reference: 1. Adelphi Respiratory Disease Specific Programme 2009. **2.** Olof Selroos et al. *Treat Respir Med* 2008; 5 (5): 305-315. **3.** Engel et al. *Br J Clin Pharmacol* 1992; 33(6): 439-44.

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1 TABLET DAILY

COMPOSITION: Triplixam 5mg/1.25mg/5mg film-coated tablets 5 mg perindopril arginine (per)/1.25 mg indapamide (ind)/5 mg of amlodipine (amlo); Triplixam 10mg/2.5mg/5mg film-coated tablets: 10 mg per/2.5 mg ind/5mg amlo; INDICATIONS: Substitution therapy for treatment of essential hypertension, in patients already controlled with perindopril/indapamide fixed dose combination and amlodipine, taken at the same dose level. DOSAGE AND ADMINISTRATION: One tablet per day, preferably in the morning and before a meal. The fixed dose combination is not suitable for initial therapy. If a change of the posology is required, titration should be done with the individual components. Paediatric population: should not be used. CONTRAINDICATIONS: Dialysis patients. Patients with untreated decompensated heart failure. Severe renal impairment (Clcr < 30 mL/min). Moderate renal impairment (Clcr 30-60 mL/min) for Triplixam 10mg/2.5mg/5mg and 10mg/2.5mg/10mg. Hypersensitivity to the active substances, to other sulphonamides, to dihydropyridine derivatives, any other ACE-inhibitor or to any of the excipients. History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy. Hereditary/idiopathic angioedema. Second and third trimesters of pregnancy (see Warnings and Pregnancy and lactation sections). Lactation (see Pregnancy and lactation section). Hepatic encephalopathy. Severe hepatic impairment. Hypokalaemia. Severe hypotension. Shock, including cardiogenic shock. Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis). Haemodynamically unstable heart failure after acute myocardial infarction. Concomitant use with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60mL/min/1.73m2) (see Warnings and Interaction(s) sections). WARNINGS: Special warnings: Neutropenia/agranulocytosis/thrombocytopenia/ anaemia: caution if collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or combination of these complicating factors, especially if pre-existing impaired renal function. Monitoring of white blood cell counts. Hypersensitivity/angioedema, intestinal angioedema: stop treatment and monitor until complete resolution of symptoms. Anaphylactoid reactions during desensitization: Caution in allergic patients treated with desensitization and avoid if venom immunotherapy. Temporarily withdrawal of ACE-inhibitor at least 24 hours before desensitization. Anaphylactoid reactions during LDL apheresis: Temporarily withholding ACEinhibitor prior to each apheresis. Haemodialysis patients: consideration to use a different type of dialysis membrane or class of antihypertensive agent. Pregnancy: no initiation during pregnancy, stop treatment and start alternative therapy if appropriate. Hepatic encephalopathy: stop treatment. Photosensitivity: stop treatment. Precautions for use: Renal function: In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show renal insufficiency, stop treatment and restart at a low dose or with one constituent only. Monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. If bilateral renal artery stenosis or single functioning kidney: not recommended. Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, in patients with low blood pressure, renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites): start treatment at low doses and increase progressively. Hypotension and water and sodium depletion: Risk of sudden hypotension in presence of pre-existing sodium depletion (in particular if renal artery stenosis): Monitoring of plasma electrolytes, re-establish blood volume and pressure, restart treatment at a reduced dose or with only one of the constituents. Sodium levels: More frequent monitoring in elderly and cirrhotic patients. Potassium levels: Hyperkalaemia: Monitoring of serum potassium if renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics, potassium supplements or potassium salts, or other drugs associated with increases in serum potassium. Hypokalaemia: risk for elderly and/or malnourished subjects, cirrhotic patients with oedema and ascites, coronary patients, patients with renal failure or heart failure, long QT interval: monitoring of serum potassium. Calcium levels: hypercalcemia: stop treatment before investigating the parathyroid function. Renovascular hypertension: if renal artery stenosis: start treatment at hospital at low dose; monitor renal function and potassium. Dry cough. Atherosclerosis: start treatment at low dose in patients with ischaemic heart disease or cerebral circulatory insufficiency. Hypertensive crisis. Cardiac failure/severe cardiac insufficiency: Caution if heart failure. Severe cardiac insufficiency (grade IV): start treatment under medical supervision with reduced initial dose. Aortic or mitral valve stenosis / hypertrophic cardiomyopathy: Caution if obstruction in the outflow tract of the left ventricle. Diabetic patients: If insulin dependent diabetes mellitus, start treatment under medical supervision with reduced initial dose; monitor blood glucose during the first month and/or in the case of hypokalaemia. Black people: higher incidence of angioedema and apparently less effective in lowering blood pressure than in non-blacks. Surgery / anaesthesia: stop treatment one day before surgery. Hepatic impairment: Mild to moderate: caution. Stop treatment if jaundice or marked elevations of hepatic enzymes. Uric acid: hyperuricemia: Increased tendency to gout attacks. Older people: testing of renal function and potassium levels before treatment start. Dosage increase with care. INTERACTION(S): Contraindicated: Aliskiren in diabetic or impaired renal patients. Not recommended: Lithium, Aliskiren in patients other than diabetic or impaired renal patients, Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker, Estramustine, Potassium-sparing drugs (e.g triamterene,amiloride,...), Potassium salts, Dantrolene (infusion), Grapefruit or grapefruit juice. Special care: Baclofen, Non-steroidal anti-inflammatory medicinal products (included acetylsalicylic acid at high doses), Antidiabetic agents (insulin, hypoglycaemic agents), Non-potassium-sparing diuretics and Potassium-sparing diuretics (eplerenone, spironolactone), Torsades de pointes inducing drugs, Amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives, Cardiac glycosides, CYP3A4 inducers, CYP3A4 inhibitors. To be taken into consideration: Imipramine-like antidepressants (tricyclics), neuroleptics, other antihypertensive agents and vasodilatators, tetracosactide, Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide, Anaesthetic drugs, Diuretics (thiazide or loop diuretics), Gliptines (linagliptine, saxagliptine, sitagliptine, vildagliptine), Sympathomimetics, Gold, Metformin, Iodinated contrast media, Calcium (salts), Ciclosporin, Atorvastatin, digoxin, warfarin or ciclosporin, Simvastatin. PREGNANCY AND BREASTFEEDING: Not recommended during the first trimester of pregnancy. Contraindicated during the second and third trimesters of pregnancy and lactation. FERTILITY: Reversible biochemical changes of spermatozoa in some patients treated by calcium channel blockers. DRIVE & USE MACHINES: May be impaired due to low blood pressure that may occur in some patients, especially at the start of treatment. UNDESIRABLE EFFECTS: Common: dizziness, headache, paresthesia, vertigo, somnolence,
dysgeusia, visual disturbances, tinnitus, palpitations, flushing, hypotension (and effects related to hypotension), cough, dyspnoea, abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, pruritus, rash, maculopapular rashes, muscle cramps, ankle swelling, asthenia, fatigue, oedema. Uncommon: eosinophilia, hypoglycaemia, hyperkalaemia reversible on discontinuation, hyponatraemia, insomnia, mood changes (including anxiety), mood disturbances, depression, sleep disorder, hypoesthaesia, tremor, syncope, diplopia, tachycardia, vasculitis, bronchospasm, rhinitis, dry mouth, altered bowel habits, urticaria, angioedema, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions, alopecia, purpura, skin discoloration, hyperhidrosis, exanthema, photosensitivity reactions, pemphigoid, arthralgia, myalgia, back pain, micturition disorder, nocturia, increased urinary frequency, renal failure, erectile dysfunction, gynaecomastia, pain, chest pain, malaise, oedema peripheral, pyrexia, weight increase, weight decrease, blood urea increased, blood creatinine increased, fall. Rare: confusion, blood bilirubin increased, hepatic enzyme increased. Very rare: agranulocytosis, aplastic anaemia, pancytopenia, haemoglobin decreased and haematocrit decreased, leucopenia, neutropenia, haemolytic anaemia, thrombocytopenia, allergic reactions, hyperglycaemia, hypercalcaemia, hypertonia, peripheral neuropathy, angina pectoris, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), myocardial infarction, possibly secondary to excessive hypotension in high risk patients, stroke possibly secondary to excessive hypotension in high-risk patients, eosinophilic pneumonia, gingival hyperplasia, pancreatitis, gastritis, hepatitis, jaundice, abnormal hepatic function, erythema multiform, Stevens-Johnson Syndrome, exfoliative dermatitis, toxic epidermic necrolysis, Quincke's oedema, acute renal failure. Not known: Potassium depletion with hypokalaemia, particularly serious in certain high risk populations, torsades de pointes (potentially fatal), possibility of onset of hepatic encephalopathy in case of hepatic insufficiency, possible worsening of pre-existing acute disseminated lupus erythematosus, electrocardiogram QT prolonged, blood glucose increased, blood uric acid increased. OVERDOSE. PROPERTIES: Perindopril is an inhibitor of the angiotensin converting enzyme (ACE inhibitor) which converts angiotensin I to angiotensin II. Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. PRESENTATION: Box of 30 tablets of Triplixam 5mg/1.25mg/5mg, and 10mg/2.5mg/5mg. LES LABORATOIRES SERVIER, 50 rue Carnot, 92284 Suresnes cedex France. www.servier.com For complete information, please refer to the Summary of Product Characteristics

1.Toth K, on behalf og the PIANIST Investigators. Am J Cardiovasc Drug 2014;14:137-145
2.Chalmers J, et al. Hypertension 2013;63:259-264