Comparative Study of the New Analgesics Tramadol, Butarphanol, Nalbuphine and Buprenorphine.

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Summary

A comparative study of tramadol, butarphanol, nalbuphine and buprenorphine was performed. The tested drugs were given as post operative analgesics after standard techniques of anaesthesia. All tested drugs were effective for post-operative pain. Buprenorphine and tramadol exhibited a longer duration of analgesia with a lesser incidence of side effects. No significant changes in vital function occured except for one severe episode of ventilatory depression with buprenorphine.

Introduction

Effective control of post operative pain is still one of the most pressing issues in surgery today. Of the millions of people which undergo surgery worldwide, most will experience pain of varying duration and intensity, which in many cases will not be adequately treated. A major objective of research in analgesics has been to find effective alternatives to morphine and meperidine (pethidine) which are free from abuse potential, tolerance, respiratory depression and tendency to cause nausea and vomiting. This goal has as yet only been partially achieved. Major advances have been made in understanding how opiates exercise their effects. There is convincing evidence for the existence of multiple opiate receptors (mu, kappa, sigma and possibly delta) and multiple modes of interaction with each type of receptor.[20,42] Although their physiological function is still obscure their study should lead towards the development of better analgesic drugs.

Methods

The drugs were tested on patients who had undergone cholecystectomy. This choice was made for various reasons: Cholecystectomy is a common operation after which, pain is usually severe and normally treated by opiate drugs. Cholecystectomy pain has been used by various centres as a model for the study of post operative pain. Patients coming for this operation are usually ASA I or II and standard techniques of anaesthesia can be used.

Pre-medication consisted of Atropine 0.5-1 mg and Pethidine 50-100mg IM up to 1 hour pre-operatively. Anaesthesia consisted of a thiopentone induction plus suxamethonium for intubation. Pipercuronium or alcuronium were used to maintain relaxation and IPPV with nitrous oxide/oxygen supplemented with Fentanyl 0.1 to 0.15mg, Droperidol 2.5mg. Relaxation was routinely antagonized at the end of the operation by standard doses of neostigmine and atropine.

The analgesics were tested in an open clinical trial. The use of placebo was considered unethical. Pain scoring was on a scale of 4.0-no pain, 1-mild pain, 2-severe pain and 3-intolerable pain. Blood pressure, heart rate and adverse effects were evaluated at regular intervals till 7.00am the next day or till post operative pain subsided.

Tramadol

This drug is derived from cyclohexanol. In experimental animals it is 3-20 times less potent than morphine. It does not depress respiration in normal dosage but tends to raise heart rate and blood pressure slightly. Tramadol has been classified as having a low risk for causing dependence.[21,30] It is effective orally and 1/3 is excreted unchanged in the urine. Tramadol has a half-life of 6 hours.

We have used Tramal 100^{R}, Grubenthal (containing 100mg tramadol hydrochloride) on 33 patients. The first dose was given as soon as verbal contact with the patient was obtained and basal

vital parameters noted. 15 and 30 minutes later further vital measurements were made. A second dose was given if the first injection proved inadequate after a 45 minute interval. After transfer to the ward, further doses of Tramal were given as required after a minimum interval of 4 hours. If pain became severe after 3 hours the patient was taken off the trial.

Results

No correlation was found between duration and quality of analgesia and patient age, weight or duration of operation. Heart rate was depressed to 70% of the previous rate in 14 patients.

Body weight mean 71,3 (range 47-100) kg
Age mean 53,3 (range 22-78) years
Duration of operation mean 63,3 (range 30-215) min
Effective duration of 1st injection 33 patients
mean 5,2(0-14) hours
Effective duration of 2nd injection 31 patients
mean 6,4(0-12) hours

Side effect	1st dose	2nd dose
Drowsiness	1	1
Nausea	1	2
Vomiting	4	2
Other (Dizziness)	1	

Nalbuphine

Nalbuphine is a thebaine derivative acting as a partial antagonist at mu and as agonist at kappa opiate receptors.[1,3,23-26,36,37,41,47] When administered alone there is a ceiling to the respiratory depression induced – but this is equivalent to that produced by 10 to 30 mg Morphine. When Nalbuphine is administered after high doses of other opiates, respiratory depression is antagonised without disturbing the continuity of the analgesia. Cardiovascular parameters remain remarkably stable after Nalbuphine. It is metabolised in the liver but partially excreted unchanged. It is thought to have no abuse potential. In this trial Nubain[R] DuPont (20mg nalbuphine hydrochloride in 2ml) was used on 33 patients. In 20 patients pre-medication was changed to Diazepam 5-10mg and Atropine (Group A). Group B had the usual Pethidine/Atropine. Nubain was given as described for Tramal but the minimum period between injections, in the ward, was reduced to 2 - 3 hours.

Results

No differences were seen between 3 groups. No relation between analgesic effect, patient body weight, age and duration of operation was noted. No adverse changes in vital functions were seen.

Body weight mean 69,9 (range 47-105) kg
Age mean 45.4 (range 28-60) years
Duration of operation mean 61,2 (range 25-125) min
Duration of analgesia after 1st injection
3,4 (0-12) hour
Duration of analgesia after 2nd injection
4,5 (0-12) hours (30 patients)

Side effect	1st injection	2nd dose
Drowsiness	8	22
Nausea	1	0
Vomiting	3	1
Other: Disorientation	1	
Allergic reaction	1	

Buprenorphine

Buprenorphine is another thebaine derivative with mixed agonist/antagonist action. It has a very high affinity but low activity at the mu receptor which is difficult to antagonize by Naloxone. Its analgesic potency is 25-40 times that of Morphine and has a longer duration of action. The respiratory depression of Buprenorphine is widely reported to have a ceiling. Some bradycardia and reduction in blood pressure is seen but is not usually clinically significant. Although no tolerance or dependence has been reported, withdrawal signs can be precipitated in patients chronically on Buprenorphine, if enough Naloxone is given. 55% of oral Buprenorphine becomes available to the tissues.[9] It is metabolised in the liver. 27% appears in the urine unchanged.

In these trials Temgesic[R] Boehringer (containing 0.3mg Buprenorphine in 1ml) was used on 18 patients. Pre-medication, anaesthesia and post operative protocol was as described for Tramadol.

Results

No relation between analgesic effect, body weight and duration of operation was found.

Body weight	mean 71,2 (range 52-90) kg
Age	mean 53 (range 30-68) years
Duration of operation	mean 64 (range 45-105) min
Duration of analgesic effect of 1st injection	7,3 (range 0-13) hours
Duration of analgesic effect of 2nd injection	8,8 (range 0-14) hours

Side effect	1st dose	2nd dose
Drowsiness	6	0
Nausea	1	1
Vomiting	0	2

There was one case of severe respiratory depression which necessitated antagonism by naloxone.

Butarphanol

This is derived from Nalorphine and is 3.5 to 5 times more potent than Morphine. Butarphanol exhibits a ceiling effect as regards respiratory depression but Naloxone is required in higher doses than usual to antagonize such effects. It may raise pulmonary artery pressures and cardiac output in some patients. While it has a marked sedative effect in most patients the risk of dependence seems to be low. Only about 20% of the agent is available to the tissues after oral administration. It is excreted in the urine after hydroxylation. Effective half life is 2,5-3 hours.[14,34,39] For these trials Stadol[R] Bristol or Butarphanol VUFB made in Czechoslovakia were used. Both have 2mg in 1ml. 36 patients were studied in the manner as described for Tramadol.

Results

No difference was found between the 2 preparations. No correlation was found between analgesic effect and body weight, age and duration of operation. No significant vital disturbances occured.

Body weight	mean 68,6 (range 46-95) kg
Age	mean 48,4 (range 26-76) years
Duration of operation	mean 54,4 (range 30-150) min
Duration of effect of 1st injection	mean 3,5 (range 0-14) hours
Duration of effect of 2nd injection	mean 4,5 (range 0-14) hours

Side effect	1st dose	2nd dose
Drowsiness	20	17
Nausea	3	0
Vomiting	5	3
Other: Dizziness	2	
headache	1	
disorientation	1	

Discussion

The attributes of an ideal analgesic may be summarised thus:

1) reliable steady effect
2) minimal disturbance of vital functions
3) no risk for abuse or decreased effectiveness from tolerance
4) simple and safe application.

All the tested drugs were effective in controlling pain after cholecystectomy. The extremes of effectiveness seen with the first dose of each drug i.e. either no effectiveness or prolonged duration of effect, highlights the great variability between patients as regards pain.

Tramadol and Bubprenorphine had a longer lasting analgesic effect and much less sedative effect than Nalbuphine and Butarphanol. Sedation is not an effect without benefit to the patient, especially immediately post operatively. However it becomes progressively less desirable in the subsequent days, as it retards the rehabilitation to normal activity.

Nausea and vomiting occured to a similar extent with all drugs (10-20%).

While a reduction in heart rate is to be expected with the start of analgesia this was actually seen only with Tramadol, so a direct action is postulated. On the other hand Butarphanol was associated with a rise in heart rate.

It is a fact that most physicians underdose when prescribing analgesics. This is mainly done in fear of respiratory depression which occured in one patient after Buprenorphine.

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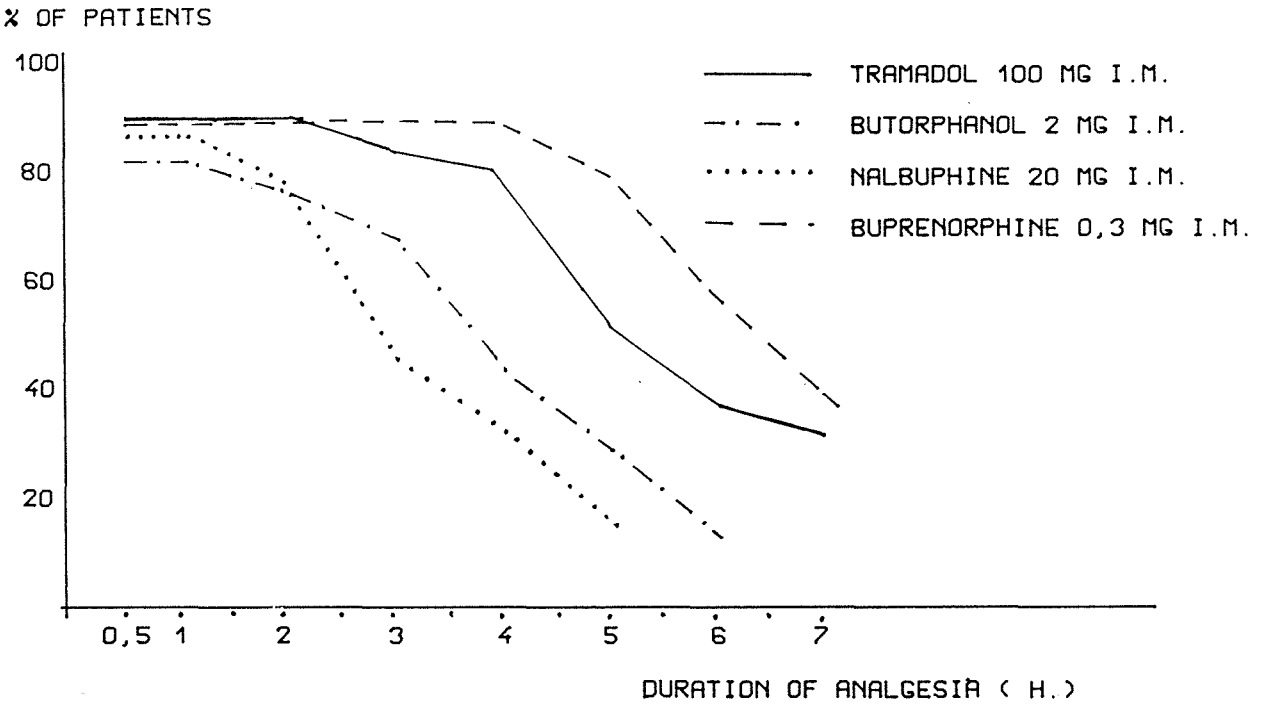
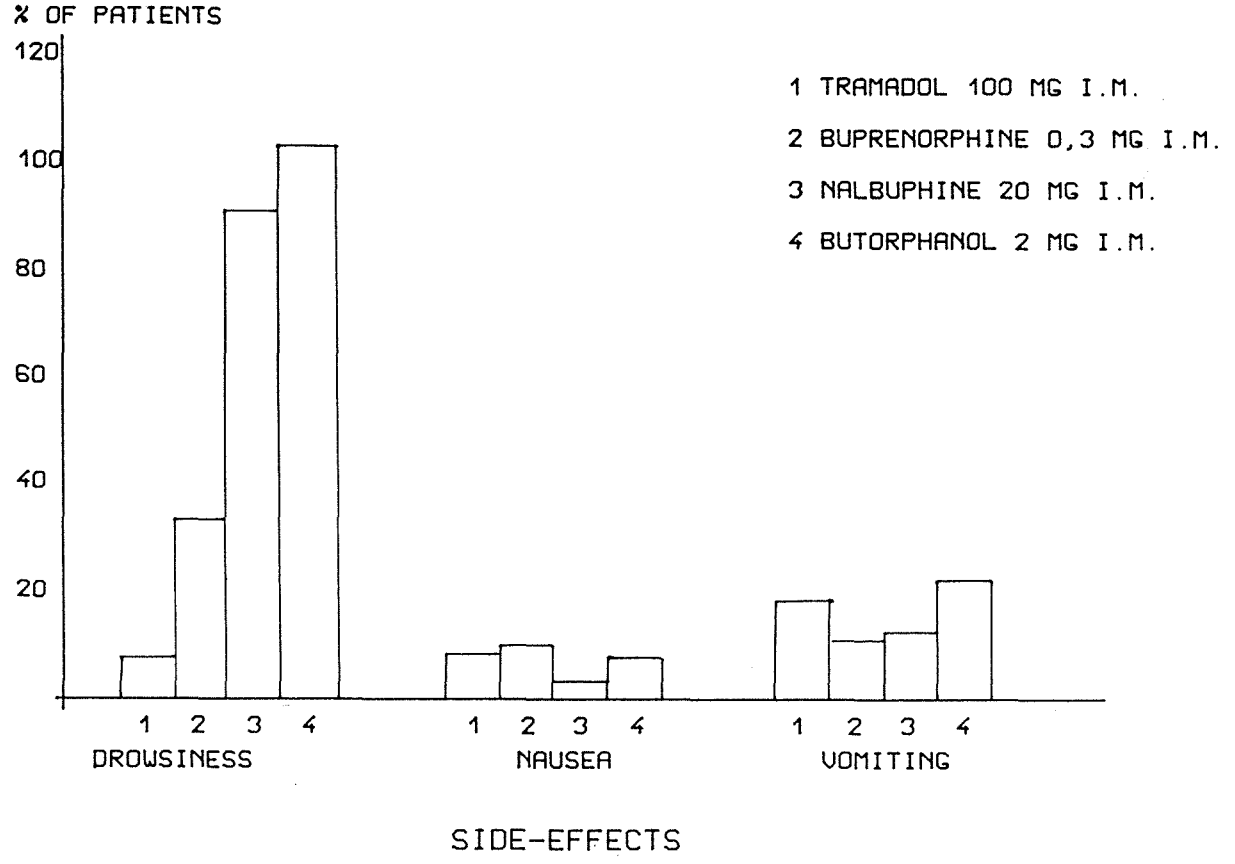

% OF PATIENTS
100
80
60
40
20
TRAMADOL 100 MG I.M.
BUTORPHANOL 2 MG I.M.
NALBUPHINE 20 MG I.M.
BUPRENORPHINE 0,3 MG I.M.
0,5 1 2 3 4 5 6 7
DURATION OF ANALGESIA (H.)


% OF PATIENTS
120
100
80
60
40
20
1 TRAMADOL 100 MG I.M.
2 BUPRENORPHINE 0,3 MG I.M.
3 NALBUPHINE 20 MG I.M.
4 BUTORPHANOL 2 MG I.M.
1 2 3 4
DROWSINESS
1 2 3 4
NAUSEA
1 2 3 4
VOMITING
SIDE-EFFECTS

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