A DOUBLE-BLIND STUDY OF THE EFFECTS OF BUTORPHANOL COMPARED WITH MORPHINE IN BALANCED ANAESTHESIA*

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BUTORPHANOL TARTRATE is an iminoethanophenanthrene compound synthesized by Monkovic, *et al.*[1] at Bristol Laboratories of Canada. It is a totally synthetic agonist-antagonist analgesic which does not require opium alkaloids for its preparation. In animals, butorphanol is substantially more potent as an analgesic than morphine, meperidine and pentazocine.[2] In man, the analgesic potency of butorphanol appears to be 5 to 8 times that of morphine sulphate,[3-5] 16 to 20 times that of pentazocine[6,7] and 30 to 50 times that of meperidine[8-9] on a per milligram basis, when injected intramuscularly or intravenously. With its combined narcotic antagonist and potent analgesic properties this drug offers promise as an analgesic with a low propensity for producing addiction and acceptable mild respiratory depression.[2,10-14]

The objective of this study was to evaluate the analgesic effect of butorphanol tartrate as compared to morphine sulphate in a double-blind study using these agents as supplements to balanced anaesthesia. The dosages of butorphanol and morphine employed in this investigation were based upon the range of analgesic potencies reported in previous studies and accord with the clinical experience of the author.

METHOD

This double-blind study evaluated the comparative utility of butorphanol tartrate and morphine sulphate as supplements to balanced anaesthesia. A total of 50 patients were studied. All patients were informed of the nature of the study and gave written consent to participate.

Patients selected for the study had not participated in any previous drug studies for at least four weeks, had no history of developed tolerance or addiction to narcotic drugs, had not received any other analgesic medication for at least 24 hours, and were classified ASA I or II physical status. All patients with a history or physical examination and laboratory tests suggesting hepatic, renal or haematological disease were excluded from the study, as were females of childbearing potential and those judged to have limited mental competence.

Identical vials containing sterile solutions of butorphanol tartrate 1 mg/ml or morphine sulphate 5 mg/ml were labeled for each patient according to a predetermined randomization schedule. A double-blind experimental design was employed. Consenting patients were entered into the study according to the randomized sequence. Approximately 25 patients were assigned to each treatment group.

A record was kept of each patient's laboratory tests performed on venous blood before and 24 hours after the operation. These included SGOT, alkaline phosphatase, total bilirubin, blood urea nitrogen and creatinine. Measurements of preoperative, intra-operative and post-operative pupillary diameter and any conjunctival changes were also recorded.

All patients received a combination of two or more agents as preoperative medication. The most frequently used agents were atropine (45 patients) and diazepam (35), with atropine and diazepam together being the most frequent combination (32 patients). In this regard, there were no apparent differences between the treatment groups.

A mean dose of butorphanol tartrate 2.0 mg or morphine sulphate 10 mg was administered two to three minutes before induction of anaesthesia with a sleep dose of thiopentone (200 to 500 mg). The patient was ventilated by mask with 100 per cent oxygen and was then given a muscle relaxant, either pancuronium (Pavulon^{R}) 4 to 9 mg, d-tubocurare (6 to 15 mg) or succinylcholine (80 to 100 mg) to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide, oxygen and multiple intravenous doses of either butorphanol or morphine.

Anaesthesia was maintained with a 50 per cent nitrous oxide, 50 per cent oxygen mixture from a

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semi-closed circuit with a two-litre per minute flow for each gas. Each patient had his ventilation controlled manually or by a respirator. Butorphanol tartrate or morphine sulphate was also employed during maintenance of anaesthesia by multiple intravenous doses.

Arterial blood gases (Pa_{CO_2}, Pa_{O_2}), pH and base excess were determined and recorded before anaesthesia and three times thereafter at the beginning of spontaneous respiration, one hour post-operatively, and 24 hours post-operatively.

To compare the effects of butorphanol tartrate and morphine sulphate on all tests and observations, the data recorded were subjected to a "t" test for two independent samples. The times in minutes from the end of anaesthesia to spontaneous respiration and to recovery of wakefulness were recorded. A record was also made of whether emergence from anaesthesia was smooth or stormy; whether respiration was adequate at the end of anaesthesia; if the non-depolarizing muscle relaxants were reversed adequately; whether the patient was extubated in the operating room; whether a narcotic antagonist was required post-operatively; the incidence of post-operative nausea and/or vomiting; the necessity and time sequence for additional use of analgesics in the post-operative period and a final subjective evaluation of the analgesic given to the patient up to 24 hours post-operatively.

The final interview with the patient noted the time interval remembered from administration of analgesic medication to loss of consciousness, the degree of amnesia from the time the patient was taken to the operating room to return to the ward after the operation and subjective evaluation by the patient of the effectiveness of the anaesthetic.

All side effects occurring in the 24-hour post-operative period were recorded as to type, frequency and relationship to study medication.

Results

Patient characteristics by treatment group are shown in Table I. Twenty-seven patients were male and 23 female. Mean age was 54 years in the butorphanol group and 51 years in the morphine group with a range from 23 to 83 years. There was little difference in age, body weight and sex between the butorphanol and morphine test groups. Most of the patients were Caucasian in both groups. The patients underwent a wide variety of procedures, the most common being cholecystectomy (11 patients), herniorraphy (7), and lumber laminectomy (5).

Evaluation conducted 60 minutes after administration of the pre-operative medication and before the administration of the study drugs showed that there were no striking differences between the two groups (Table II).

Induction of anaesthesia was initiated either with butorphanol tartrate (mean dose 2.0 mg) or morphine sulphate (10 mg). Vital signs were noted for a 3-minute period after the test dose. The induction of anaesthesia was then completed in 48 patients with a sleep dose of thiopentone in a dose range of 200 to 500 mg and in 2 patients with intravenous diazepam 0.25 mg/kg. The mean dose and range for each drug are shown in Table III. On the average, each patient received either 4.6 mg butorphanol tartrate or 22.8 mg morphine sulphate for maintenance. The average total dose per patient was 6.6 mg for butorphanol tartrate and 32.8 mg for morphine sulphate.

Arterial blood gases, pH and base excess were not appreciably altered by either of the analgesics (Table IV and Table V).

The evaluation of anaesthesia showed that the induction and course were satisfactory in most of the patients in both groups. The analgesic was not discontinued in any case and no other agent was substituted for the test drug in any patient of either group. The mean duration of anaesthesia was 163 minutes in the butorphanol group with a range of 48 to 320 minutes and 160 minutes in the morphine group with a range of 35 to 380 minutes.

Emergence from anaesthesia was uncomplicated in all patients but was judged as slow in three patients who received butorphanol tartrate and eight who received morphine sulphate. The mean time in minutes for the end of anaesthesia to spontaneous respiration in the butorphanol group was 10 minutes with a range of 4 to 25 minutes (std. dev. 6), while in the morphine group the mean time was 12 minutes with a range of 0 to 25 minutes (std. dev. 7). Mean time to awakening was 21 minutes in the butorphanol group with a range of 6 to 45 minutes (std. dev. 11), and 23 minutes in the morphine group with a range of 5 to 55 minutes (std. dev. 12). These differences are not statistically significant.

Emergence from anaesthesia was rated as smooth in all patients of both groups. Respiration was inadequate for extubation at the end of anaesthesia in eight per cent of both test groups. The muscle relaxants were reversed with neostigmine in 64 per cent of the butorphanol group and in 72 per cent of the morphine group. Of the

TABLE I

DEMOGRAPHIC CHARACTERISTICS

	Age (years)			Weight (kg)	Sex		Race	
	23–60	61–83	Mean	Mean	Male	Female	White	Black
Butorphanol Tartrate	16 (66%)	9 (44%)	54	73 (45–100)	14 (56%)	11 (44%)	23 (92%)	2 (8%)
Morphine Sulphate	19 (76%)	6 (24%)	51	74 (45–125)	13 (52%)	12 (48%)	20 (80%)	5 (20%)

TABLE II

PRE-OPERATIVE MEDICATION

		Butorphanol tartrate	Morphine sulphate
Drowsiness	None	0	5 (20%)
	Slight	13 (52%)	10 (40%)
	Moderate	12 (48%)	10 (40%)
	Marked	0	0
Apprehension	None	9 (36%)	9 (36%)
	Slight	7 (28%)	12 (48%)
	Moderate	7 (28%)	1 (4%)
	Marked	2 (8%)	3 (12%)
Excitement	None	13 (52%)	20 (80%)
	Slight	11 (44%)	3 (12%)
	Moderate	1 (4%)	2 (8%)
	Marked	0	0

TABLE III

STUDY MEDICATION/DOSAGE INFORMATION

	Butorphanol tartrate			Morphine sulphate		
	n	Mean (mg)	Range (mg)	n	Mean (mg)	Range (mg)
Test medication	25	2	2–3	25	10	10–10
Thiopentone	23	300	200–500	25	290	150–500
Pancuronium	14	7	5–9	11	6	4–9
Succinylcholine	10	94	80–100	11	95	80–100
d-Tubocurare	2	8	3–12	5	7	3–15
Diazepam	2	15	10–20	0	—	—

INDUCTION AND MAINTENANCE/DOSAGE CHARACTERISTICS OF TEST MEDICATIONS

	Butorphanol tartrate	Morphine sulphate
Total patients	25	25
Total mg administered	166.0	820.0
Average mg/patient	6.64	32.80
Time between doses (min.)	11	12

TABLE IV

SUMMARY OF ARTERIAL BLOOD GASES BEFORE AND AFTER BALANCED ANAESTHESIA WITH BUTORPHANOL TARTRATE

	Before anaesthesia		Beginning spontaneous breathing		After anaesthesia: 1 hour		After anaesthesia: 24 hours	
H^+ nmol/l/pH	H^+ nmol/l	pH	H^+ nmol/l	pH	H^+ nmol/l	pH	H^+ nmol/l	pH
Mean ± S.E.	39 ± 1	7.41 ± 0.01	40 ± 2	7.40 ± 0.02	43 ± 1	7.37 ± 0.01	42 ± 1	7.38 ± 0.01
Range	45–34	7.35–7.47	55–26.8	7.26–7.57	51–34.4	7.29–7.47	48–36	7.32–7.45
Pa_{CO_2}	kPa	Torr	kPa	Torr	kPa	Torr	kPa	Torr
Mean ± S.E.	4.12 ± 0.12	37 ± 1	4.92 ± 0.21	37 ± 1.6	5.19 ± 0.15	39 ± 1.1	5.19 ± 0.15	39 ± 1.1
Range	3.19–6.52	24–49	2.93–6.52	22–49	3.99–7.05	30–53	3.72–6.78	28–51
Pa_{O_2}								
Mean ± S.E.	10.77 ± 0.53	81 ± 4	17.82 ± 1.73	134 ± 13	14.36 ± 1.33	108 ± 10	9.98 ± 0.27	75 ± 2
Range	7.32–19.95	55–150	7.58–42.56	57–320	7.85–36.6	59–275	8.1–12.37	16–93
Base excess mmol/l	−1		−2		−3		−2	

TABLE V

SUMMARY OF ARTERIAL BLOOD GASES BEFORE AND AFTER BALANCED ANAESTHESIA WITH MORPHINE SULPHATE

	Before anaesthesia		Beginning spontaneous breathing		After anaesthesia: 1 hour		After anaesthesia: 24 hours	
H^+ nmol/l/pH	H^+ nmol/l	pH	H^+ nmol/l	pH	H^+ nmol/l	pH	H^+ nmol/l	pH
Mean ± S.E.	39 ± 1	7.41 ± 0.01	40 ± 2	7.40 ± 0.02	42 ± 1	7.38 ± 0.01	42 ± 1	7.38 ± 0.01
Range	47–35	7.33–7.46	56–24	7.25–7.62	58–28	7.27–7.55	49–37	7.31–7.44
Pa_{CO_2}	kPa	Torr	kPa	Torr	kPa	Torr	kPa	Torr
Mean ± S.E.	5.05 ± 0.09	38 ± 0.7	4.92 ± 0.24	37 ± 1.8	5.33 ± 0.19	40 ± 1.4	5.19 ± 0.09	39 ± 0.7
Range	4.92–5.99	33–45	3.59–7.85	27–59	2.79–7.45	21–56	4.92–5.99	33–45
Pa_{O_2}								
Mean ± S.E.	10.91 ± 0.53	82 ± 4	14.63 ± 1.06	110 ± 8	13.03 ± 0.8	98 ± 6	10.64 ± 0.26	80 ± 2
Range	5.99–19.68	45–148	7.71–30.59	58–230	8.11–22.34	61–168	8.78–13.57	66–102
Base excess mmol/l	−		−2		−2		−2	

patients studied, only one of the butorphanol group was not extubated in the operating room at the end of the procedure and required ventilatory assistance in the recovery room. One patient of the butorphanol group and five of the morphine group required naloxone to augment pulmonary ventilation. The analgesic was rated effective in 88 per cent of the butorphanol group and in 92 per cent of the morphine patients. It was moderately effective in the remainder. In none was the analgesic ineffective.

Side effects were experienced by two patients who received butorphanol tartrate. One patient had post-operative nausea and vomiting. Another patient had inadequate respiration post-operatively. One patient who received morphine had severe post-operative respiratory depression, while another who received morphine had slow respiration.

There were no significant electrocardiographic changes during operation or post-operatively in the recovery room.

Analgesic medication was required by seven of the butorphanol patients and five of the morphine patients in the immediate post-operative period.

At the post-operative visit 24 hours after the operation a questionnaire was completed for each patient regarding induction, amnesia and recovery-room events. In the butorphanol group, 40 per cent could remember nothing, 56 per cent noted a short time for induction and one patient (4 per cent) noted a very long induction period. A similar distribution was recorded for the morphine group. In the butorphanol group 68 per cent of the patients had total amnesia for the period in the operating suite while 32 per cent had some degree of amnesia. In the morphine group 76 per cent of patients had total amnesia, while 20 per cent had some amnesia. One patient (4 per cent) had no amnesia. None of these differences were statistically significant.

Discussion

The clinical assessment of any medication given during operation is difficult because of its qualitative nature and subjectivity. No single evaluation scheme is devoid of criticism. Such evaluations during operation are further complicated by differences in surgical procedures, duration of operation, patient variables and study conditions.[15]

The use of parenteral narcotic analgesics in balanced anaesthesia is a well-recognized technique. Many previous studies have shown butorphanol tartrate to be a potent analgesic offering excellent pain relief[3-9] and the duration of action in every respect approximates that of morphine sulphate.[3-5,16] The present study demonstrates that butorphanol tartrate in divided doses of 1 to 2 mg is comparable to the intermittent intravenous use of morphine sulphate 5 to 10 mg in a balanced anaesthesia technique with nitrous oxide and oxygen, with a low incidence and severity of side effects and satisfactory amnesia. This conclusion agrees with that of Dobkin, *et al.*,[16] who evaluated butorphanol as an analgesic in balanced anaesthesia in an open experimental design.

Summary

In a randomized double-blind trial a total of 50 consenting patients scheduled for elective surgical operations were given multiple intravenous doses of butorphanol tartrate or morphine sulphate in combination with other agents to evaluate and compare the efficacy of these drugs in balanced anaesthesia.

Equipotent doses of butorphanol tartrate (mean dose 2.0 mg) or morphine sulphate (10 mg) and thiopentone were employed as induction agents followed by the standardized use of muscle relaxants to facilitate tracheal intubation. Butorphanol tartrate or morphine sulphate were then employed during maintenance of anaesthesia in repeated intravenous doses, averaging butorphanol 4.6 mg and morphine 22.8 mg per patient. Evaluation of anaesthesia showed that induction and course were smooth in 96 per cent of the patients receiving butorphanol tartrate and in 84 per cent of patients receiving morphine sulphate. The analgesic action of butorphanol appeared in every respect to approximate that of morphine sulphate, with negligible side-effects. The data demonstrate that butorphanol is a useful analgesic for use in a balanced anaesthesia technique with a low side-effect incidence.

Résumé

Le tartrate de butorphanol et le sulfate de morphine ont été comparés chez 50 patients soumis à une chirurgie majeure sous anesthésie balancée, au cours d'une étude à double insu. Des doses de puissance équivalente, soit 2 mg de butorphanol et 10 mg de morphine, ont été administrées par voie intraveineuse, deux ou trois minutes avant une dose hypnotique de thiopenthal et un curarisant pour l'intubation. Puis, l'un ou l'autre des

narcotiques ont été utilisés en doses fractionnées au besoin, pour supplémenter le protoxyde d'azote et les curarisants (doses moyennes totales: 4.64 mg de butorphanol par patient versus 22.8 mg pour la morphine).

L'induction a été jugée facile et sans problèmes chez 96% des malades ayant reçu du butorphanol et chez 84% de ceux du groupe à qui l'on a administré de la morphine. De même, on a jugé que le maintien de l'anesthésie était satisfaisant et sans problème chez tous les patients du groupe "butorphanol" et chez 95% de ceux du groupe "morphine". L'analgésie produite par le butorphanol a semblé équivalente à celle produite par la morphine. Les effets secondaires ont été minimes.

Nos résultats démontrent que le butorphanol peut être un agent utile au cours d'anesthésies balancées, avec une basse incidence d'effets secondaires.

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