A CLINICAL INVESTIGATION OF PIRITRAMIDE IN THE TREATMENT OF POSTOPERATIVE PAIN

BY

B. KAY

SUMMARY

In a double-blind trial three dosage strengths of piritramide, 5, 10 and 20 mg, were compared with morphine 15 mg in the treatment of postoperative pain. Pain intensity was assessed by the patient, and pain relief and side effects by a nurse-assessor. A log-dose response relationship was established for piritramide. Piritramide 20 mg was shown to be equivalent to morphine 15 mg in analgesic effect. From this and previous studies of piritramide, it appears that piritramide has a greater hypnotic effect than an equi-analgesic dose of morphine, but that it has a lesser incidence of other side effects, particularly nausea and vomiting, and hypotensive effects. Piritramide is indicated as a suitable analgesic for postoperative pain relief.

Piritramide is a tertiary amine of the diphenylpropylamine series shown to have an intense analgesic action comparable with morphine (Janssen, 1961). Clinical effectiveness was demonstrated by Weyne, Schluter and Lust (1968), Henschel, Buhr and Fernandez (1968) and Saarne (1969) who indicated a long duration of action, and a low incidence of nausea and vomiting.

The present study was planned as a dose-response study of piritramide, examining also the duration of action of the drug and the incidence of side effects compared with morphine 15 mg.

METHOD

The investigation was conducted as a between-patient, single-dose, double-blind trial. It included 240 patients with postoperative pain of a type and severity for which an intramuscular narcotic is usually given. The patients were given one intramuscular injection of trial medication when the need for a postoperative analgesic became apparent, and each patient received one dose only. Thereafter standard postoperative analgesic therapy was continued.

Four medications were included in the trial. They were piritramide 5 mg, piritramide 10 mg, piritramide 20 mg, and morphine 15 mg. They were prepared so as to be identical in appearance and were in individual dose ampoules for administration in random order, with sixty patients receiving each medication during the course of the study.

Clinical information was obtained and recorded in a similar way to that previously reported by Parkhouse, Collie and Wood (1967). Two state-registered nurses acted as clinical assessors. Before the medication was given each patient was asked to grade his pain as none (0), mild (1), moderate (2) or severe (3). Patients with moderate or severe pain were given a trial medication. The same assessor then visited the patient after half an hour, an hour, then hourly up to 6 hours. At each visit the patient was asked to grade his pain in the same way as before, and the assessor also recorded her own impression of the pain relief obtained, none (0), poor (1), moderate (2) or good (3). A non-specific request concerning the occurrence of side effects was also made at each visit, and any objectively apparent complications were noted. The severity of side effects was recorded as mild (1), moderate (2) or severe (3).

After the observations were completed, or earlier if the effect of the trial drug was insufficient, the patient was discharged from the study and normal postoperative pain relief measures instituted. All data were recorded on a clinical investigation card (Parkhouse, 1967), together with all relevant information concerning the patient, date and time of trial drug administration, previous and concurrently administered drugs, site and nature of pain.

B. KAY, M.B., CH.B., F.F.A.R.C.S., D.A., Derbyshire Royal Infirmary, Derby, DE1 2QY.
Patients were not included in the trial if they weighed less than 55 kg or more than 85 kg. Other specific exclusions were pregnant or nursing females, patients with respiratory, cardiac, renal or hepatic insufficiency, known drug addicts and patients with any disability affecting complete communication between subject and assessor.

All patients included had given informed consent, were suffering from moderate or severe postoperative pain and were in a physical and clinical condition such that they were fit to receive an intramuscular injection of morphine 15 mg. This eliminated all poor-risk and debilitated patients, and the necessity to adjust trial medication dosage to body weight or surface area. It was assumed that individual variation in the size of sample taken would permit statistical analysis of results.

RESULTS
Scores considered valid for pain intensity and relief were obtained for all 240 patients. Patients requiring a further dose of analgesic and withdrawn from the trial were regarded as having severe pain (3) and no pain relief (0) for the rest of the observation period. In the four groups the age and weights of the patients were evenly matched, and there was a fairly even distribution of the sexes, although the morphine group included more females. Group 1 received piritramide 5.0 mg (mean 0.075 mg/kg); group 2, piritramide 10 mg (mean 0.15 mg/kg); group 3, piritramide 20 mg (mean 0.3 mg/kg); and group 4, morphine 15 mg (mean 0.225 mg/kg).

Figures 1 and 2 show in graphic form the mean pain intensity for each group, before and after medication, and the mean pain relief obtained. It is seen that all the medications produced on average a satisfactory (moderate to good) degree of relief during the period of observation, and that pain intensity was considerably reduced. It is also apparent that increasing the dosage of the piritramide increased its analgesic effectiveness, and that piritramide 20 mg was indistinguishable in its effects from morphine 15 mg, as judged by this assessment.

Figures 3 and 4 show the log-dose/response regressions for the analgesic action of piritramide with morphine 15 mg providing a reference point closely corresponding with that of piritramide 20 mg. The graphs were constructed from the results obtained at 1 and 2 hours after administration, whilst the drugs were producing their maximal effect. In each case the points lie close to a straight line and statistical analysis shows a significant regression. Application of Student's t test to the responses to piritramide 5 mg and piritramide 20 mg show a highly significant difference (P<0.01).

Figure 5 shows the number of patients in each group requiring a further dose of postoperative analgesic. This indication of the end of adequate analgesic action shows clearly the increased incidence of short effective action with the smaller doses of piritramide, and is the only indication in this study of a difference in analgesic effect between morphine 15 mg and piritramide 20 mg.

Side effects were rare in all groups. Figure 6 shows the relative incidence of those most
PIRITRAMIDE IN THE TREATMENT OF POSTOPERATIVE PAIN

1.2
1.0
0.8
0.6

I
X PIRITRAMIDE
O MORPHINE

FIG. 3

Log-dose/response (patient's assessment) regression for piritramide. Mean pain intensity scores, with standard errors, taken at peak response time (1 and 2 hours after injection). The mean response to morphine 15 mg provides a reference point.

Regression of log-dose of piritramide (X) on pain intensity (Y)

\[ Y = 0.789X + 1.717 \]

(0.230) (0.237)

Figures in brackets indicate the related standard error.

frequently observed, nausea and vomiting and sleepiness. It suggests that piritramide has a slightly more hypnotic and slightly less emetic effect than morphine.

DISCUSSION

Choice of method.

The assessment of subjective and objective relief of postoperative pain is an acceptable method of comparison of the analgesic potency of drugs, particularly when postoperative pain relief is one of the main areas of application of the drugs under investigation. The method of assessment and recording used is an established one, and the clinical assessors had undergone a period of training in the use of the method in similar circumstances, comparing pethidine with a placebo. As other comparisons between piritramide and a placebo have been published (Weyne,
Schluter and Lust, 1968; Feifel and Thurmayr, 1970) and the main purpose of this study was to establish a dose-response curve and comparison with morphine, it was considered unnecessary to include a placebo in our circumstances.

Results obtained.

The results obtained were similar to those obtained with piritramide for postoperative pain in previous assessments. Lund and colleagues (1965) found piritramide 15 mg somewhat less effective than morphine 10 mg. Saarne (1969) used piritramide in doses of 10–20 mg, usually 15 mg, after which 96 per cent patients were judged to have “sufficient” pain relief. He assessed the duration of action as 6 hours 20 min ± 9.1 min. Henschel, Buhr and Fernandez (1968) used piritramide 10–15 mg (on average 0.21 mg/kg), with good analgesia in 90 per cent of patients, and adequate analgesia in 7 per cent. In this series the estimated duration of action was 4 hours 41 min after the first dose, and 6 hours 28 min after the second. Weyne, Schluter and Lust (1968) used piritramide 15 mg and obtained complete pain relief in 78 per cent and some effect in 20 per cent of his patients. These estimates are compatible with the present results although we would agree with Nilsson (1966, personal communication) that the standard dose of piritramide for an adult should perhaps be 20 mg.

Concerning side effects, great stress has been laid in previous studies on the low incidence of vomiting after piritramide, quoted variously as 1 per cent (Saarne, 1969), 1 case in 552 patients (Henschel, Buhr and Fernandez, 1968), 0 in 1866 patients (Nilsson, E., 1966, personal communication), and 2 in 99 patients (Weyne, Schluter and Lust, 1968). The incidence in our study was less than with morphine, but not so low as in previous reports. However, many of Nilsson’s and Henschel’s patients had received droperidol. Weyne, Schluter and Lust, and Saarne give no indication of their use of anti-emetics.

The other main side effect apparent in our study of piritramide was sleepiness, especially after the largest dose. Previous investigations again give a similar picture. Thus Saarne states, “the patients often sank into a light sleep”, and Henschel reports that “usually they reported mild sleepiness”. Delooze and Van De Walle (1968) state that the hypnotic effect was marked.

Other workers investigating specific side effects of piritramide have concluded that the respiratory depressant effect of piritramide 20 mg is less than that of morphine 15 mg (Saarne, 1969), and that the effect on the blood pressure is negligible in patients with a normal cardiovascular system, and small in patients with an unstable circulation (Henschel, Buhr and Fernandez, 1968). Piritramide 15 mg depressed the systolic blood pressure significantly less than hydromorphone 2 mg (Feifel and Thurmayr, 1970).

ACKNOWLEDGEMENTS

I would like to thank Professor J. Parkhouse for his assistance with the design of this study, Sisters Latham and Morley for their work as nurse-assessors, and the medical and nursing staff of the Derby hospitals for their assistance. The investigation was supported by a grant from Janssen Pharmaceuticals for the salaries of the nurse-assessors.

REFERENCES


ETUDE CLINIQUE DE L’EMPLOI DE LA PIRITRAMIDE EN VUE DU TRAITEMENT DES DOULEURS POST-OPERATOIRES

SOMMAIRE

Dans le cadre d’un essai en double-avéu, on a procédé à l’étude comparative de trois dosages différents de piritramide: 5, 10 et 20 mg, avec l’administration de 15 mg de morphine, en vue du traitement d’algies post-opératoires. L’intensité de la douleur a été appréciée par le malade, alors que la suppression de celle-ci, de même que les effets secondaires étaient objectivés par
PIRITRAMIDE IN THE TREATMENT OF POSTOPERATIVE PAIN 1171

une infirmière. On a procédé à l'établissement d'une
relation logarithmique entre la dose administrée et la
réponse thérapeutique, en ce qui concerne la piritra-
mide. L'administration de 20 mg de piritramide s'est
avérée présenter un effet analgésique équivalent à une
dose de 15 mg de morphine. Sur la base de cette étude,
ainsi que des travaux précédemment effectués sur la
piritramide, il apparait que cette substance est douée
d'un effet hypnotique supérieur à celui d'une dose
equi-analgésique de morphine, mais qu'elle suscite les
autres effets secondaires tels que nausées, vomissements
et chutes tensionnelles suivant une fréquence moindre.
La piritramide est indiquée en tant qu'agent anal-
gésique convenant au traitement des algies post-
opératoires.

KLINISCHE UNTERSUCHUNG VON
PIRITRAMID IN DER BEHANDLUNG
POSTOPERATIVER SCHMERZEN

ZUSAMMENFASSUNG
In einem Doppelblind-Versuch wurden drei verschie-
dene Dosen von Piritramid (5, 10 und 20 mg) mit 15
mg Morphin in der Behandlung postoperativer Schmer-
zen verglichen. Die Schmerzintensität wurde von den
Patienten selbst, Schmerzmilderung und Nebenwirk-
ungen von einer Pflegeperson eingestuft. Für Piritra-
mid wurde eine Dosis-Wirkungskurve aufgestellt. Die
analgetische Wirkung von 20 mg Piritramid entsprach
der von 15 mg Morphin. Zusammen mit früheren

Untersuchungen ergeben sich Hinweise, daß Piritramid
eine stärkere hypnotische Wirkung als eine aqui-
analgetische Dosis Morphin besitzt, dafür aber andere
Nebenwirkungen, vor allem Nausea, Erbrechen und
Hypotonie schwächer ausgeprägt erscheinen. Piritramid
wird als geeignetes Analgeticum zur postoperativen
Schmerzbehandlung empfohlen.

INVESTIGACION CLINICA DE LA
PIRITRAMIDA EN EL TRATAMIENTO
DEL DOLOR POSTOPERATORIO

RESUMEN
Tres niveles de dosificación de piritramida, 5, 10 y 20
mg, fueron comparados en una prueba doblemente ciega
cona 15 mg de morfina para el tratamiento del dolor
postoperatorio. La intensidad del dolor fue estimada
por el paciente y el alivio del dolor y efectos secundarios
por una enfermera asesoradora. Fue establecida una
relación log-dosis respuesta para la piritramida. Se
demostró que 20 mg de piritramida tienen un efecto
analgésico equivalente a 15 mg de morfina. De este y
estudios anteriores sobre la piritramida se deduce que
la piritramida tiene un efecto hipnótico mayor que una
dosis equi-analgesica de morfina, pero que presenta
una frecuencia menor de otros efectos secundarios,
especialmente de náusea y vómitos y efectos hipoten-
sores. La piritramida está indicada como analgésico
decuado para aliviar el dolor postoperatorio.

FACULTY OF ANAESTHETISTS
ROYAL COLLEGE OF SURGEONS IN IRELAND

PRIZE ESSAY

The Board of the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland
invites any postgraduates, up to the grade of Senior Registrar, working in anaesthesia in
Ireland, to submit an essay on a subject related to anaesthesia.

A prize of thirty pounds will be awarded to the best entry. Entries which should pre-
ferably be based on personal investigations by the candidate should be sent to the
Honorary Secretary, Board of the Faculty of Anaesthetists, Royal College of Surgeons
in Ireland, Stephen’s Green, Dublin 2, so as to reach him not later than Thursday,
April 20, 1972.