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Double-blind crossover trial of oral meptazinol, pentazocine and placebo in the treatment of pain in the elderly

V. PEARCE
M.B. B.S., M.R.C.P.

P. J. ROBSON
M.B. B.S., M.R.C.P.

Chesterton Hospital, Cambridge and Wyeth Laboratories, Maidenhead, Berkshire

Summary

In a randomized, double-blind crossover trial in 30 elderly patients suffering from moderate to severe pain, the analgesic efficacy, tendency to produce mental confusion and side effect profile of meptazinol 100 mg orally were compared with those of pentazocine 25 mg orally and placebo.

Both the active drugs produced significantly better analgesia than placebo but meptazinol also provided significantly better pain relief than pentazocine, whilst at the same time causing less mental confusion. Side effects were unremarkable.

Meptazinol appears to be a better general purpose oral analgesic in this group of patients than pentazocine.

Introduction

It is commonly found that when it is necessary to use a strong analgesic such as an opiate or pentazocine in an elderly person there is a high incidence of adverse CNS effects such as confusion, agitation or hallucinations and these are clearly detrimental both to the patient and to the running of the ward.

Meptazinol is a novel benzomorphan compound with partial opiate-antagonist properties which has been shown to be equivalent in analgesic potency at a dose of 100 mg to pethidine 100 mg (Paymaster, 1977; A. Hedges (personal communication); M. B. A. Jackson and P. J. Robson (personal communication), papaveretum 20 mg (Moyer, Miller and Aldridge, 1979) and pentazocine 60 mg (Paymaster, 1977), all drugs given i.m. It is free from anti-5-hydroxytryptamine and anti-cholinergic activity and in clinical trial has shown a low incidence of CNS side effects. An additional factor in the group of patients is meptazinol's favourable respiratory profile (Jordan *et al.*, 1979).

An open pilot study in 11 patients revealed that meptazinol 100 mg orally gave satisfactory pain relief and was well tolerated, so it was therefore decided to compare the compound for efficacy and side effect incidence with the oral analgesic most frequently used for moderate to severe pain in the unit, pentazocine 25 mg orally, and placebo. The 2 active drugs were given in deliberately small doses as it is well recognized that age is highly correlated with the pain relief obtained from a given dose of analgesic (Bellville *et al.*, 1971) and that the elderly are more susceptible to drugs in general (Leading Article, 1977).

Materials and methods

This was a randomized double-blind crossover trial in 30 patients over the age of 70 years who had given informed consent to participate and who would in any case have required a potent oral analgesic. Eighteen patients were female, and the mean age was $81{\cdot}4 \pm 6{\cdot}4$ years.

TABLE 1. Painful conditions for which analgesia was required

Fractured neck of femur
Paget's disease
Intractable headaches of unknown origin
Seronegative arthritis
Rheumatoid arthritis
Osteoporosis
Osteomalacia
Bony secondaries
Carcinoma of pancreas
Carcinoma of caecum
Large pressure sores
Dislocated acromioclavicular joint
Spondylosis
Angina pectoris
Carcinoma of breast
Multiple pyarthrosis
Carcinoma of prostate
Fractured ankle

On admission to the study, all analgesics and non-essential drugs were discontinued and each patient was randomly allocated to either Group A, Group B or Group C. The painful conditions for which the patients required relief are shown in Table 1. Each patient then received in random order placebo, meptazinol 100 mg and pentazocine 25 mg according to the following routine.

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On admission to the trial, and when an analgesic was requested by the patient, the pain intensity score was measured using a visual analogue scale, and the mental state assessed by the 'E' test. In this test, the patient is given a typewritten passage of writing which contains 50 letter 'E's, and is asked to read through the piece crossing out the 'E's, thereby obtaining a score out of 50. A different passage is used for each assessment, and it is generally accepted that performance in this test correlates well with the degree of mental confusion. Other observations made at this time included pulse rate, BP and the presence or absence of any other symptoms such as nausea and vomiting. Test drug no. 1 was then given, and the above observations repeated at 30 min, one hr, 2 hr, and 4 hr. When next the patient requested an analgesic, an identical procedure was adopted for test drug 2 and likewise for test drug 3. In the event of analgesia being inadequate during an observation period, the pain intensity for unmeasured time-points was adjudged as the maximum, 10, and the next test drug was given according to the randomized schedule. Blood samples for the measurement of meptazinol concentration in plasma were taken at the observation time-points from some patients in the trial.

Results

Open pilot study

Eleven patients suffering from moderate to severe pain of various aetiologies received 100 mg meptazinol by mouth, and an 'E' test and pain intensity scored by visual analogue scale were measured at the following time-points; 0, 30 min, 1, 2, 3, and 4 hr. The mean results for the group are illustrated graphically in Fig. 1. Whereas mean pain intensity is significantly reduced from 30 min onwards ($P < 0{\cdot}025$–Wilcoxon matched pairs signed rank test), the fluctuations in 'E' score do not reach statistical significance.

Double-blind study

The pain intensity difference and 'E' scores are displayed graphically as group means in Figs 2 and 3. Pain intensity difference is obtained by subtracting the pain intensity at the various time-points from the pre-treatment pain intensity for each individual.

Both meptazinol and pentazocine gave significant pain relief at all times over the 4-hr period in comparison with placebo, and meptazinol gave significantly better pain relief than pentazocine at one and 2 hr after dosing. At 3 and 4 hr, the pain relief afforded by the 2 active agents did not significantly differ.

Pentazocine depressed the 'E' score significantly more than meptazinol throughout the 4-hr period and indeed meptazinol differed from placebo in this regard at the 2-hr time-point only.

None of the test drugs had any significant effect on BP or pulse rate, and the side effect profile is shown in Table 2.

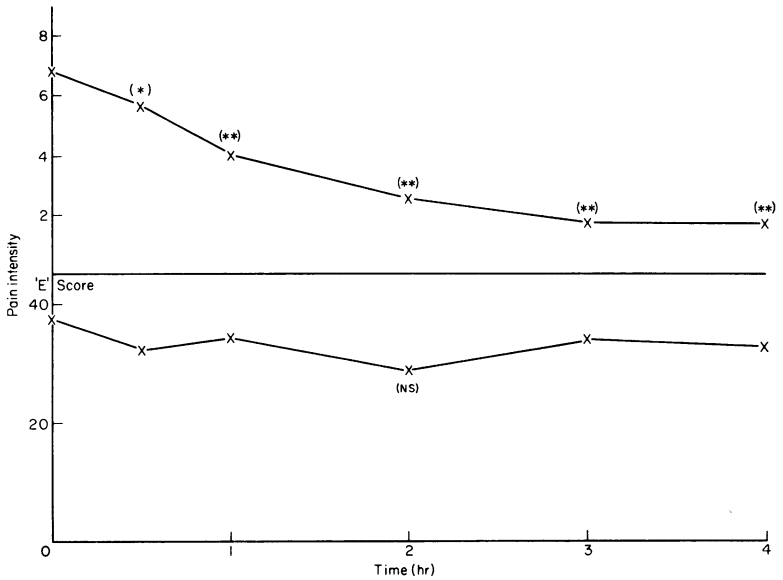

FIG. 1. Results of open pilot study. Comparison with base line. (*) P, 0·025; (**) P, 0·005; (NS) not significant.

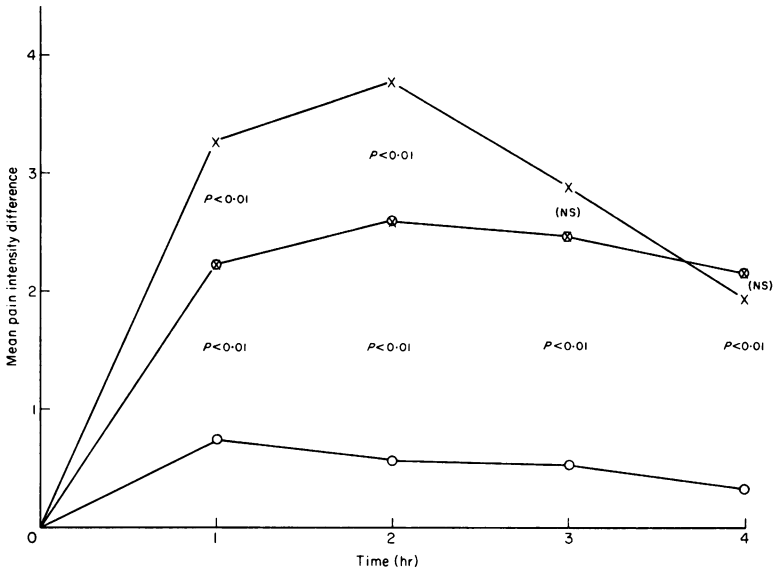

FIG. 2. Group mean pain intensity differences. ×——× metazinol 100 mg; ⊗——⊗ pentazocine 25 mg; ○——○ placebo.

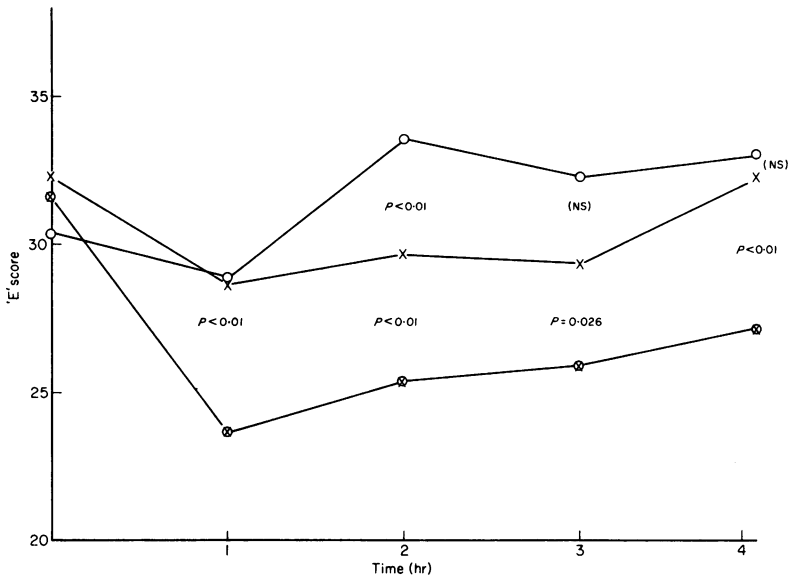

FIG. 3. Group mean 'e' scores.

TABLE 2. Side effects

Side effect	Placebo	Meptazinol	Pentazocine
Nausea and vomiting	0	2	0
Nausea alone	0	1	1
Dizziness	1	0	0

Peak plasma concentrations tended to occur at 2–3 hr after dosing, and the mean plasma concentration at this time in a group of 12 patients was 20·1 ± 17·3 (s.d.) ng/ml.

Discussion

Adverse reactions to drug therapy in the elderly are a major cause of morbidity. Important predisposing factors are age and sex; significantly more patients aged 60 years and over, and more women than men develop adverse reactions (Hurwitz, 1969).

Neurological and mental disturbances due to drug therapy are extremely common in the elderly, who are particularly susceptible to centrally acting drugs. The reactions seen include mental confusion, disorientation, hallucinations, fluctuating levels of awareness and depression (Davison, 1978). The elderly metabolize many drugs more slowly than do the young, and plasma half-lives for a given dose are prolonged (O'Mally *et al.*, 1971).

The chief factors involved seem to be a reduced lean body mass and a substantial pre-existing impaired function of certain organs and systems, especially the central nervous, respiratory and cardiovascular systems, and the kidneys. In the case of potent analgesics, the elderly are prone to confusion and disorientation particularly if there is some prior erosion of mental reserve, and respiratory depression is a special hazard. Because gut transit times are often greatly prolonged in these patients, constipation is a frequent problem, and this is likely to be exacerbated by a number of analgesics.

Meptazinol has a favourable respiratory profile in comparison with morphine and pentazocine (Jordan *et al.*, 1979; Verschraegen *et al.*, 1976). Constipation has not been reported following its oral or parenteral administration in man. In animal studies, meptazinol caused less gastrointestinal inhibitory activity than equi-analgesic doses of morphine or pentazocine (Stephens, Waterfall and Franklin, 1978). As with other strong analgesics, meptazinol may induce nausea and vomiting, and this was seen in the study in low incidence, albeit more commonly than with pentazocine (Table 2).

In this group of patients meptazinol produced significantly better pain relief than did either pentazocine or placebo. Although the level of awareness as judged by the 'E' test was lower following meptazinol than that following placebo, it remained significantly superior to that following pentazocine for the entire period studied. No patient was noticeably confused or obtunded at the doses used.

In this group of very elderly patients in whom depression of awareness rapidly leads to deterioration of bladder control, diminution of mobility to pressure necrosis of skin, and constipation to discomfort and eventual overflow incontinence of faeces, the potential advantage of an effective analgesic agent attended by a diminished incidence of these problems is self-evident.

Conclusion

The present trial demonstrates that oral meptazinol offers advantages over pentazocine in the routine treatment of moderate to severe pain in the elderly.

The relief of pain by meptazinol as judged by a visual analogue scale was significantly better than that following pentazocine.

Awareness was significantly less impaired by meptazinol than by pentazocine.

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