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TOOTH PULP STIMULATION: A METHOD OF DETERMINING THE ANALGESIC EFFICACY OF MEPTAZINOL IN MAN

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A dose-ranging study of meptazinol was carried out using the pain threshold to electrical tooth pulp stimulation in healthy volunteers as the pain model. A well defined dose-response curve was found for oral meptazinol (50 mg, 100 mg, 150 mg and 200 mg) and placebo. The methodology and results are discussed in terms of subsequent clinical experience with meptazinol.

Introduction

The validity of using healthy volunteers for the evaluation of the efficacy of novel analgesics has been discussed in recent reviews. Littlejohns & Vere (1981) in their excellent treatise, differentiated between the 'pain sensation' associated with experimentally induced stimulation and 'pain suffering' which is prevalent in the clinical forum and is characteristically linked with anxiety, anger and/or depression. Because these psychological attenuators of the pain experience vary so considerably among patients, the extent to which one may extrapolate measured reduction in 'pain sensation' (experimental situation) to a reduction in 'pain suffering' is debatable.

The extant literature contains equivocal reports regarding the reproducibility of results in volunteer studies (Wolff, 1978; Lasagna, 1980). However, Gabka (1971, 1972) found that, as a pain model, tooth pulp stimulation provided both repeatable results and good correlation between experimental and clinical analgesia.

This study was designed to elicit a dose response curve for meptazinol (an oral hexahydroazepine analgesic) using tooth pulp stimulation in healthy human volunteers. The results are discussed in terms of subsequent clinical experience with the drug.

Methods

Measurement of analgesic efficacy was carried out using the method of Gabka (1971, 1972).

A copper ring individually made for each subject, was affixed to an upper incisor tooth and an indifferent electrode applied to the forearm skin *via* metal arm bands soaked in saline. For each subject, the same tooth was used in each assessment. The basal pain threshold for each patient was determined by applying a small increasing current to the tooth and assessing the intensity (milliamperes—mA) at which the subject felt the first trace of pain (usually a tingling sensation). The pain threshold was reassessed at 2, 5, 7, 10, 12, 15, 20, 25, 30, 40, 50, 60, 75, 90, 120, 180 and 240 min after drug administration and was categorised thus:

Elevation in pain threshold (mA)	*Analgesic response*
10	Threshold
11–15	Weak
16–25	Good
26–30	Very good
>30	Excellent

The ten healthy volunteers (five male, five female) used in the study were aged between 16 and 48 years. They were not allowed to smoke, drink alcohol nor take any other drugs for at least 24 h prior to each test. A light meal was given 90 min before recordings.

Each of the subjects received five oral treatments (placebo, 50, 100, 150 and 200 mg meptazinol) in a single-blind randomised fashion. All assessments were carried out with the subjects in a sitting position and blood pressure was monitored throughout the experiments on a Hartmann Electronic BP recorder.

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Results

Data pertaining to the evaluation in pain threshold were subjected to means and moments analysis. As the data were found to be normally distributed they were analysed using three way ANOVA. All interactions [time, dose and increase in pain threshold (Δt)] were highly significant. The effect of each dose over time was analysed and again there was a highly significant variation over time in every treatment group.

There was no significant ($P > 0.05$) difference in the pretreatment pain thresholds either between patients or within patients on the different assessment days. Variation between doses at each time point was assessed using 2 way ANOVA and there was no significant difference between treatments at 2, 5, 7 or 15 min. There was, however, significant variation at 10 and 12 min ($P < 0.05$), 25 min, 4 h ($P < 0.01$) and 20, 30, 40 and 50 min, 1, 1.25, 2 and 3 h ($P < 0.001$).

Figure 1 represents the difference in pain threshold compared to placebo at each time point. Although represented here as having no effect, analysis of the placebo response showed a significant variation in Δt with time. The peak placebo effect occurred at 40 min and corresponded to a weak analgesic response (13.2 mA). In contrast, there was a well defined analgesic response to the active treatments with the maximum mean increases in pain threshold of 17.4 mA (good), 24.4 mA (good); 25 mA (good) and 30.6 mA (excellent) following, 50, 100, 150 and 200 mg meptazinol respectively.

In order to define the nature of the dose response, the area under the curve (AUC) relative to placebo was calculated for each patient. The mean (± s.d.) AUC was 636.9 ± 678.8, 1849 ± 733.5*, 2003.7 ± 881.4* and 2989.3 ± 1045.5 (*NS, $P > 0.05$) for 50, 100, 150 and 200 mg meptazinol respectively. The AUC was plotted against dose giving a linear curve of $y = 14.42x + 67.15$ ($r = 0.965$; $P < 0.05$).

During the course of the trial only one patient experienced a drug related adverse reaction. This

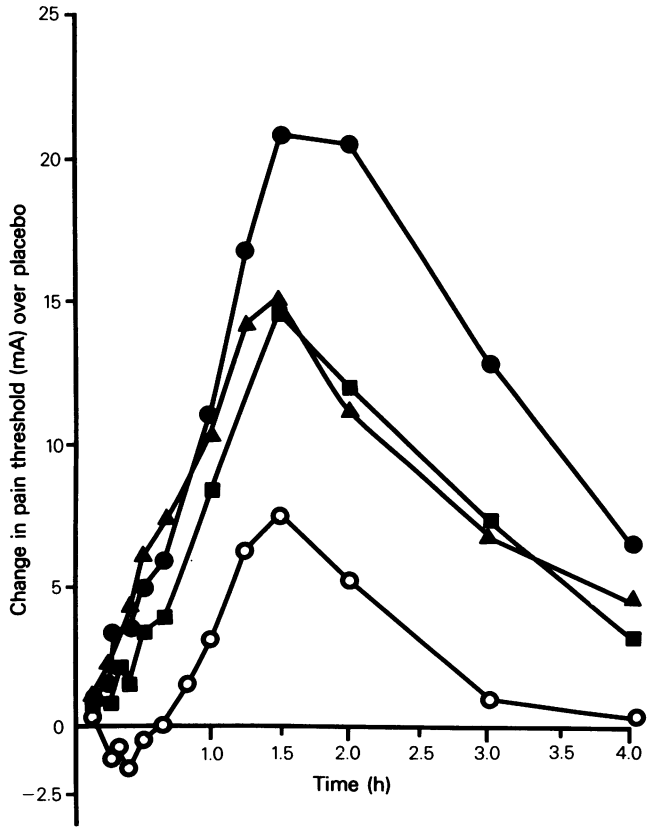

Figure 1 Mean elevation in pain threshold (mA) over the placebo response against time. ○ meptazinol 50 mg, ■ meptazinol 100 mg, ▲ meptazinol 150 mg and ● meptazinol 200 mg.

patient had transient fainting and nausea after a 200 mg dose of meptazinol. There were no significant ($P > 0.05$) changes in blood pressure at any of the concentrations used.

Discussion

The study fulfilled its role in that it provided information on the efficacy of meptazinol in man. The design was sensitive enough to differentiate not only active and placebo responses, but also to give a clearly defined linear dose-response curve. The inclusion of a placebo group obviated the problem of time-associated changes within patients (Lasagna, 1980).

The onset and duration of action of meptazinol was shown to be a function of dose, with 200 mg providing significantly better pain relief than placebo after 20 min. The time to maximal response (apparently independent of dose) was 90 min which coincides with the time (1.5–2 h) of peak plasma levels (Stephens *et al.*, 1978).

Subsequent clinical experience with meptazinol has shown 50 mg not to be an efficacious dose (data on file) and that a 100 mg dose provided good pain relief in the elderly (Pearce & Robson, 1980). Meptazinol (200 mg) was found to be an effective dose (equivalent to pentazocine 50 mg, Flavell-Matts & Ward, 1980; and 2 tablets 'Distalgesic', Wade & Ward, 1981) for patients in the age range 18–65 years).

Studies in human volunteers are usually carried out at the beginning of a drug's life span and therefore it is only in *retrospect* that the initial studies can be validated. It is clear from this work, that as a method of evaluation of the analgesic efficacy of novel compounds, tooth pulp stimulation provides good correlation between experimental and clinical usage.

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