

RESPIRATORY AND METABOLIC EFFECTS OF ORAL NEFOPAM IN HUMAN VOLUNTEERS

Nefopam hydrochloride is an analgesic whose structure is unrelated to either the opioid or anti-pyretic analgesics. Some clinical trials have compared the analgesic activity of nefopam to the narcotic analgesics (Sunshine & Laska, 1975; Tigerstedt, Sipponen, Tammisto & Turunen, 1977) and thus interest has been focused on possible respiratory depressant effects of nefopam, since this is the principal disadvantage of opioid analgesics. Gasser & Bellville (1975) investigated the respiratory effects of parenteral nefopam in human subjects and found that it caused little depression of the ventilatory response to CO₂ when examined as mean effects in six volunteers. However, there was considerable variation in response and the authors felt that nausea induced by nefopam may have caused hyperventilation, thus causing some underestimation of the respiratory depressant effects of this drug.

The side effects of nefopam are less when the drug is administered orally (Gassell, Diamantopoulos, Petropoulos, Hughes, Fernandez Ballesteros & Re, 1976). Thus the present study was designed to assess the effects of two oral doses of nefopam on the ventilatory response to CO₂.

A number of investigators have found that nefopam produced sweating and flushing (De Thibault de Boesinghe, Van Daele & Van Severen, 1976; Tigerstedt, Tammisto & Leander, 1979; Schietzel, 1977) and so the effects of nefopam on oral temperature were monitored.

Twelve healthy volunteers took part in the study (Table 1). Smokers were asked to refrain from smoking on the day of the trial and all volunteers were

asked to refrain from alcohol on the day of the trial and the preceding evening. On the day of the trial the subjects were asked to have a light breakfast at least 2 h before the commencement of the trial and after administration of the drug they were not allowed to eat or drink anything except for water for 3 h. At least 1 week elapsed between successive tests.

Before administration of any drugs control values were obtained in a number of tests. Systolic and diastolic arterial pressures were measured using a standard mercury column sphygmomanometer. The same arm was used for all readings and the same observer made all the measurements. Heart rate was measured by counting the radial pulse.

A bell closed circuit spirometer (Ealing Biosciences) with the cylinder filled with air, was used to measure tidal volume, minute volume and respiratory frequency. Gases were sampled at the mouth piece and measured continuously by an infra red CO₂ analyser (Morgan) before being returned to the circuit. The CO₂ analyser was connected to a Rikadenki single channel pen recorder so that end tidal P_{CO₂} could be read off. The ventilatory response to CO₂ was measured using the same apparatus and the method was similar to that described by Pleuvry & Maddison (1980).

Body temperature was taken using a standard clinical thermometer placed under the tongue for at least two minutes. Pain threshold was measured by a method based on Kunkle (1949). The whole hand was immersed in a bucket of iced water which was maintained at 0°C by addition of crushed ice and stirring continuously. The same hand was used for all

Table 1 Details of volunteers

Volunteer	Sex	Age (years)	Weight (kg)	Smoking habits	Alcohol consumption	Drugs
1	F	27	63.5	20/day	None	Oral contraceptives
2	F	27	63.5	20/day	Moderate	None
3	M	28	70.0	None	None	None
4	F	30	60.5	None	Rarely	Oral contraceptives
5	F	20	54.0	20/day	Moderate	None
6	M	26	68.0	None	Occasional	None
7	F	46	54.0	None	Occasional	None
8	F	37	63.0	None	Moderate	None
9	F	35	60.0	None	Moderate	None
10	M	28	72.0	None	None	None
11	M	28	60.0	15/day	Moderate	None
12	F	25	52.5	None	Occasional	Oral contraceptives

measurements and the end point was taken when the subject felt that the sensation of cold had just turned to pain.

Placebo, 30 mg nefopam or 60 mg nefopam was allocated to the subjects on a double blind basis. After administration of the tablets oral temperature was measured at 0.5, 1.5, 2.5 and 5 h. Blood pressure, pulse, pain threshold and respiratory measurements were repeated at 1, 2, 3 and 5 h. Any subjective comments were noted down.

Nefopam caused no significant changes in blood pressure, pulse rate or respiratory measurements breathing air. However the ventilatory response to CO₂ was affected by nefopam administration. One and two hours after administration of 30 mg nefopam, the slope of the ventilatory response to CO₂ was reduced (Table 2), although this effect of nefopam was not dose dependent. Displacement of the CO₂ response line only reached a significance of $P > 0.05 < 0.1$ in the number of subjects tested. However when the subjects responses to placebo and the two doses of nefopam were examined as a whole, nefopam caused a dose dependent displacement of the CO₂ response line (mean slope \pm s.e. mean $+ 0.0132 \pm 0.0054$).

Oral temperature was depressed in a dose dependent manner by nefopam (Figure 1). The fall was maximal at 1.5 h, but subjects given 60 mg nefopam still had temperatures significantly lower than placebo treated subjects 5 h after administration.

We were surprised to find that nefopam caused no significant changes in pain threshold although the variability of the responses was considerably greater in nefopam treated subjects than in placebo treated subjects.

Most subjects were unable to say on which occasion they had had the drug and the only effect which reached statistical significance ($P < 0.01$; χ^2 test) was the complaint of a dry mouth. No subject reported this side effect in the placebo group, whilst 7 subjects out of 24 reported a dry mouth after nefopam. One subject showed an extreme reaction to 60 mg nefopam (subject 12). One hour after ingestion of the

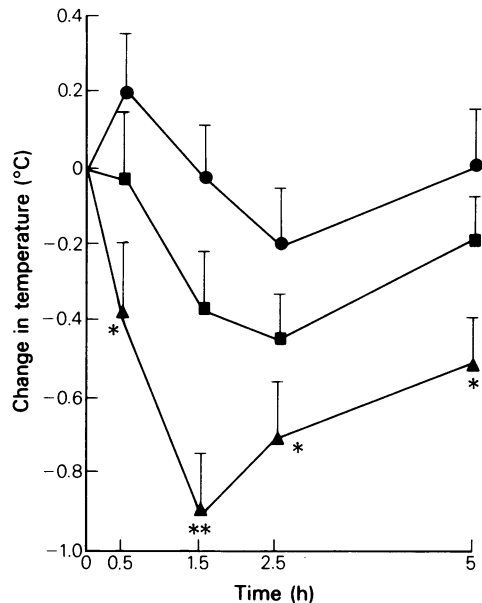


Figure 1 The effect of nefopam on the oral temperature of volunteers. Placebo orally ●, nefopam 30 mg orally ■, nefopam 60 mg orally ▲. Results are means \pm s.e. mean for twelve subjects (* $P < 0.05$; ** $P < 0.01$). Significant differences between groups (analysis of variance).

drug the subject felt tingling in her extremities, nausea, cold, palpitations and a sensation of panic. When she felt able to connect herself to the spirometer she had a respiratory frequency of 30 and a mean tidal volume of 150 ml. In the control situation this subject had a respiratory frequency of 14 and a tidal volume of 540 ml.

After the trial several volunteers claimed that they found difficulty in eating mainly because the food 'laid heavily in the stomach'. Subsequently it emerged that these delayed comments only occurred after nefopam days.

Table 2 Effect of placebo, nefopam 30 mg and nefopam 60 mg orally on the ventilatory response to CO₂ measured using a rebreathing method

Treatments	Changes in slope (l kPa ⁻¹)				Displacement (kPa) at 30 l			
	1h	2h	3h	5h	1h	2h	3h	5h
Placebo	+1.024	+0.718	+0.539	+1.272	-0.053	-0.046	-0.175	+0.058
Nefopam 30 mg	-2.831*	-4.510*	-2.562	-1.509	+0.145	+0.687	+0.187	+0.250
Nefopam 60 mg	-1.456	-2.311	-2.407	-2.262	+0.252	+0.861	+0.510	+0.935
F	3.61	4.80	0.51	1.69	0.56	1.15	3.14	1.73
Significance (d.f. 2 and 33)	$P < 0.05$	$P < 0.05$	NS	NS	NS	NS	$P > 0.05 < 0.1$	NS

Results are mean values for 12 volunteers

* Means significantly different from placebo values.

The effects of nefopam on the ventilatory response to CO₂ when given, in this study, by the oral route were much greater than those reported by Gasser & Bellville (1975) who administered the drug intramuscularly. However increasing the dose of nefopam did not increase the severity of the respiratory depression. Clinical studies on the analgesic action of nefopam have also suggested that increasing the dose of nefopam does not necessarily increase its maximum effect (Tigerstedt *et al.*, 1977; Tigerstedt *et al.*, 1979). Depression of the CO₂ response by nefopam suggests that it might enhance the respiratory depressant effects of other drugs, for example the narcotic analgesics. Animal studies have already suggested that this is the case (Stainthorp, Morton & Pleuvry, 1980).

Another positive finding of this study is that nefopam can reduce oral temperature. Since other investigators have reported sweating and flushing with nefopam (De Thibault de Boesinghe *et al.*, 1976; Tigerstedt *et al.*, 1979; Schietzel, 1977) it may be that nefopam causes an imbalance on the side of heat loss mechanisms. This requires more detailed investigation.

On the negative side, we have found that, given orally, nefopam has no significant effects upon pulse and blood pressure. This contrasts with reports concerning the parenteral use of the drug where increases

in pulse rate (Tigerstedt *et al.*, 1977; Tigerstedt *et al.*, 1979) and blood pressure (Dodson, 1980) have been observed.

Although numerous authors have found that nefopam is effective in pathological pain (Cohen, 1974; Workmon & Winter, 1974), we were unable to demonstrate that it had any significant effects upon pain threshold in volunteers. However, Wolff, Kantor, Jarvik & Laska (1966) observed that morphine 10 mg i.m. did not affect pain threshold when examined with this test although it did increase pain tolerance. In man pain threshold changes do not appear to be adequate predictors of analgesic activity.

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ASHA M. BHATT, BARBARA J. PLEUVRY & STEPHANIE E. MADDISON

Department of Anaesthetics and Pharmacology, University of Manchester, Oxford Road, Manchester M13 9PT

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References

- COHEN, A. (1974). Nefopam hydrochloride for pain relief. *Curr. Ther. Res.*, **16**, 184–193.
- DE THIBAUT DE BOESINGHE, L., VAN DAELE, M.J. & VAN SEVEREN, G. (1976). Open study of the analgesic effects of nefopam hydrochloride (Acupan) on cancer patients with pain. *Curr. Ther. Res.*, **20**, 59–61.
- DODSON, M.E. (1980). Effects of intraoperative nefopam (Acupan). *Br. J. Anaesth.*, (In press).
- GASSELL, M.M., DIAMANTOPOULOS, E., PETROPOULOS, V., HUGHES, A.C.R., FERNANDEZ BALLESTEROS, M.L. & RE, O.N. (1976). Controlled clinical trial of oral and parenteral nefopam hydrochloride. A novel and potent drug. *J. clin. Pharmac.*, **16**, 34–42.
- GASSER, J.C. & BELLVILLE, J.W. (1975). Respiratory effects of nefopam. *Clin. Pharmac. Ther.*, **18**, 175–179.
- KUNKLE, E.C. (1949). Phasic pains induced by cold. *J. appl. Physiol.*, **1**, 811–824.
- PLEUVRY, B.J. & MADDISON, S.E. (1980). A sex difference in the effects of oral codeine and promethazine on the ventilatory response to carbon dioxide in human volunteers. *Br. J. clin. Pharmac.*, **9**, 159–164.
- SCHIETZEL, VON M. (1977). Analgesie mit geringen nebenwirkungen. *Fortschritte der Medizin*, **95**, 2743–2746.
- STAINTHORP, S.F., MORTON, A.K. & PLEUVRY, B.J. (1980). The effects of nefopam on blood acid base status in the rabbit: Interactions with morphine in the mouse and rabbit. *J. Pharm. Pharmac.*, **32**, 689–692.
- SUNSHINE, A. & LASKA, E. (1975). Nefopam and morphine in man. *Clin. Pharmac. Ther.*, **18**, 530–534.
- TIGERSTEDT, I., SIPPONEN, J., TAMMISTO, T. & TURUNEN, M. (1977). Comparison of nefopam and pethidine in post-operative pain. *Br. J. Anaesth.*, **49**, 1133–1138.
- TIGERSTEDT, I., TAMMISTO, T. & LEANDER, P. (1979). Comparison of the analgesic dose-effect relationships of nefopam and oxycodone in postoperative pain. *Acta Anaesth. Scand.*, **23**, 555–560.
- WOLFF, B.B., KANTOR, T.G., JARVIK, M.E. & LASKA, E. (1966). Response of experimental pain to analgesic drugs. 1. Morphine, aspirin and placebo. *Clin. Pharmac. Ther.*, **7**, 224–238.
- WORKMON, F.C. & WINTER, L. (1974). A clinical evaluation of nefopam hydrochloride (Acupan): A new analgesic. *Curr. Ther. Res.*, **16**, 609–616.