Modification of the analgesic action of pethidine and morphine by three opiate antagonists, a respiratory stimulant (doxapram) and an analeptic (nikethamide); a study using an experimental pain stimulus in man

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The ability to antagonize opiate-induced respiratory depression without affecting analgesia would be of considerable clinical value. This paper reports studies carried out with clinically used doses of three opiate antagonists—nalorphine, levallorphan and naloxone, a new effective respiratory stimulant—doxapram, and an established analeptic—nikethamide, with respect to their influence on the analgesic action of pethidine and morphine. It is a continuation of work reported by Hamilton *et al.* (1967).

Sensitivity to pain was measured by the manual application of a measurable pressure to the anterior surface of the tibia, noting two end points: (a) first appreciation of any pain and (b) unbearable pain. The applications, limitations and expected range of observer error of this method of algesimetry have been studied in detail by Dundee and Moore (1960). Preinjection control readings were carried out in duplicate or triplicate and patients were excluded from the study if these lay outside the accepted range of individual variation. Algesimetry readings were carried out at 1–2 min intervals for up to 10 min after the test drug was given.

Drugs were given intravenously and observations were carried out in a quiet room on subjects of both sexes. Doses were calculated on a weight basis and are expressed as the equivalent for a 60 kg subject. In the first part of the study a demonstrable degree of analgesia was induced by 100 or 200 mg pethidine and the test drug injected 5 min later. (Doses employed were nalorphine 10 mg, levallorphan 1–2 mg, naloxone 0·4 mg, doxapram 60 mg, nikethamide 250 mg). The second part was carried out using a 'double blind technique', 10 mg morphine being given alone or premixed with nikethamide, doxapram or naloxone. A placebo (saline) group was included in this part of the study. Each drug combination was given to 8–10 subjects. The incidence of significant changes in the average of the two end-point readings is presented and the statistical significance of the findings determined by Fisher's exact probability test.

All three opiate antagonists markedly reduced, or in some instances abolished, pethidine-induced analgesia. The overall effect was related to the relative dose of agonist and antagonist and was most marked and prolonged when 2 mg levallorphan was given after 100 mg pethidine. Pethidine-induced analgesia was abolished temporarily by nikethamide but not affected by doxapram.

Analgesia was demonstrated in a significantly smaller number of subjects after morphine-naloxone than after morphine alone. Antagonism of morphine analgesia by nikethamide was very transient while doxapram had no detectable effect on the analgesic action of the opiate.

Doxapram has been given in combination with postoperative analgesics and preliminary results suggest that it does not interfere with pain relief in a clinical situation.

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Ascorbic acid and cholesterol mobilization by fenfluramine

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On a scorbutic diet, guinea-pigs initially gain weight before weight loss occurs; females can make metabolic readjustments so that they maintain higher tissue ascorbic acid

(AA) concentrations and survive longer than males (Odumosu & Wilson, 1971). AA plays an important role in the anti-obesity action of fenfluramine (Wilson and Odumosu, 1972), and so its effect has been investigated on changes in fat metabolism. Four groups of male and female guinea-pigs received scorbutic diets for 24 days after an initial maintenance period (Odumosu & Wilson, 1970). Individual groups received 30 (mg/kg)/day supplementary ascorbic acid subcutaneously (S), supplementary ascorbic acid and fenfluramine 15 (mg/kg)/day (SF), fenfluramine alone (F), or no treatment (Sc), The effect of fenfluramine was compared on change in weight, plasma and tissue AA, cholesterol and triglyceride concentrations (Table 1).

Both sexes gained weight significantly on the supplemented diet. Administration of fenfluramine caused loss of weight in the males. Weight gain was significantly reduced among the treated, in comparison with the untreated, supplemented, females. Fenfluramine caused similar changes in the scorbutic animals, in whom overall weight loss occurred.

In both sexes, supplemented and scorbutic, fenfluramine administration was associated with significantly lower liver AA concentrations, the effect being more evident in the males. In the supplemented animals, hepatic cholesterol was significantly higher in the male fenfluramine treated group. In the scorbutic groups, plasma and hepatic cholesterol values were significantly lower when fenfluramine was administered. Fenfluramine reduced triglyceride values in scorbutic, but had little effect in supplemented animals. During fenfluramine administration, male weight gain is more retarded, but AA catabolism is enhanced in both sexes. When AA is available, fenfluramine administration is associated with raised cholesterol, when AA is deficient, hepatic cholesterol is reduced.

TABLE 1 *The effect of fenfluramine (F) on guinea-pig tissues (mean and standard deviations) after 24 days on a scorbutic diet (Sc) on a normal ascorbic acid intake (S). Significance of difference between normal and fenfluramine treated animals at $p < 0.05$ indicated*

	Normal intake					
Tissue values	Males			Females		
	S	FS	Sig	S	FS	Sig
Body wt. (g)	564±19	470±42	S	524±46	469±35	S
Plasma AA (mg/100 ml.)	1·40±0·09	1·05±0·15	S	1·89±0·13	1·05±0·15	S
Liver AA (mg/100 g)	31·2±2·1	9·6±1·4	S	34·7±4·4	18·2±2·0	S
Plasma chol. (mg/100 ml.)	150±15	115±30	S	124±15	150±14	S
Liver chol. (mg/100 g)	522±51	802±54	S	375±39	553±83	S
Plasma triglyc. (mg/100 ml.)	102±19	103±13	NS	125±18	122±18	NS
Liver triglyc. (mg/100 g)	1,859±104	1,626±173	S	1,969±137	1,954±167	NS
	Scorbutic					
Tissue values	Males			Females		
	Sc	FSc	Sig	Sc	FSc	Sig
Body wt. (g)	406±32	343±35	S	463±33	382±47	S
Plasma AA (mg/100 ml.)	0·22±0·07	0·30±0·11	S	0·58±0·11	0·39±0·12	S
Liver AA (mg/100 g)	6·0±1·1	3·2±0·9	S	12·2±2·2	9·3±2·4	S
Plasma chol. (mg/100 ml.)	240±28	73±15	S	179±19	108±23	S
Liver chol. (mg/100 g)	1,089±118	387±69	S	744±102	393±79	S
Plasma triglyc. (mg/100 ml.)	144±5	86±5	S	172±15	104±9	S
Liver triglyc. (mg/100 g)	1,304±288	1,312±80	NS	1,386±135	1,250±124	S

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The effect of glibenclamide on two enzymes important in gluconeogenesis

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Glibenclamide is a new and very potent hypoglycaemic sulphonylurea. The main mode of action of this latter group of drugs is now commonly accepted as being to