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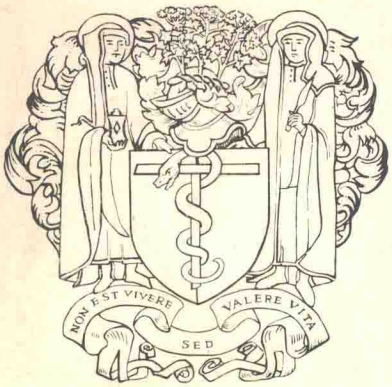

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Series·Number 3

STRESS-FREE ANAESTHESIA

Analgesia and the Suppression of Stress Responses

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Analgesia and the Suppression of Stress Responses

Edited by
C. WOOD

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Stress-free Anaesthesia

Analgesia and the Suppression of Stress Responses

Proceedings of an International Symposium held by the Janssen Research Foundation at Beerse, Belgium on 10 February 1978

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Chairman's Introduction

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In the past decades several techniques have been developed in anaesthesia which make use of intravenous compounds. Among these techniques, neuroleptanalgesia or NLA has become popular, mainly because of the stable situation created by this technique. More recently, however, several anaesthesiologists have changed the NLA technique to some extent by decreasing the doses of droperidol or even deleting droperidol altogether, whilst significantly increasing the dose of fentanyl, even up to 25–50μg/kg i.v.

Invariably, new techniques prompt queries and with regard to high doses of fentanyl several questions can certainly be raised. For example, why is this technique better than classical NLA and how sure are we that giving high doses of fentanyl really produces a distress-free situation? Indeed, how do we measure distress? It is also necessary to enquire about muscle relaxation and hypnosis with this technique and a last very practical question concerns post-operative assisted ventilation and hence the applicability of the technique in a general hospital setting.

These papers answer at least some of these questions, because the contributors are all experts in the field and have experience, both with classical NLA techniques and with relatively high doses of fentanyl.

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The Pharmacology and the Pharmacokinetics of Fentanyl

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With the chemical structure of morphine in mind, a very large number of chemical congeners have been synthesized and screened for analgesic properties. The route to highly potent synthetic opiates, however, was uncovered with the discovery that pethidine, originally designed as an atropine-like agent, possessed analgesic activity but with a potency of 0·5 of that of morphine in animal experiments. The chemical structure shows similarity with the structure of morphine (Fig. 1). A considerable increase in potency (2× morphine) was obtained with the reversed ester, in which

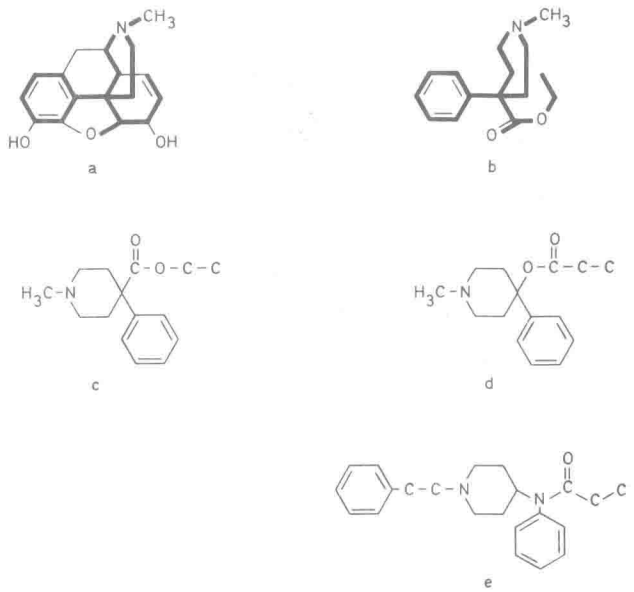

Figure 1. Chemical structure of: (a) morphine, (b, c) pethidine, (d) reversed ester of pethidine, (e) fentanyl.

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the C=O group and the O atom of pethidine were switched. Both compounds have a slow onset and a prolonged duration of action, because the speed of their passage through lipid membranes (which is dependent on the ratio of lipid solubility to water solubility) is comparatively small.

In fentanyl, a chemical congener of the reversed ester (Fig. 1), this ratio is shifted towards a higher value by an increase of lipid solubility. When the ratio reaches an optimal value, penetration through physiological lipid barriers is very rapid and the result is a rapid onset and a limited duration of action, when the drug is not specifically bound and retained by the target tissue. Easy penetration through lipid barriers also

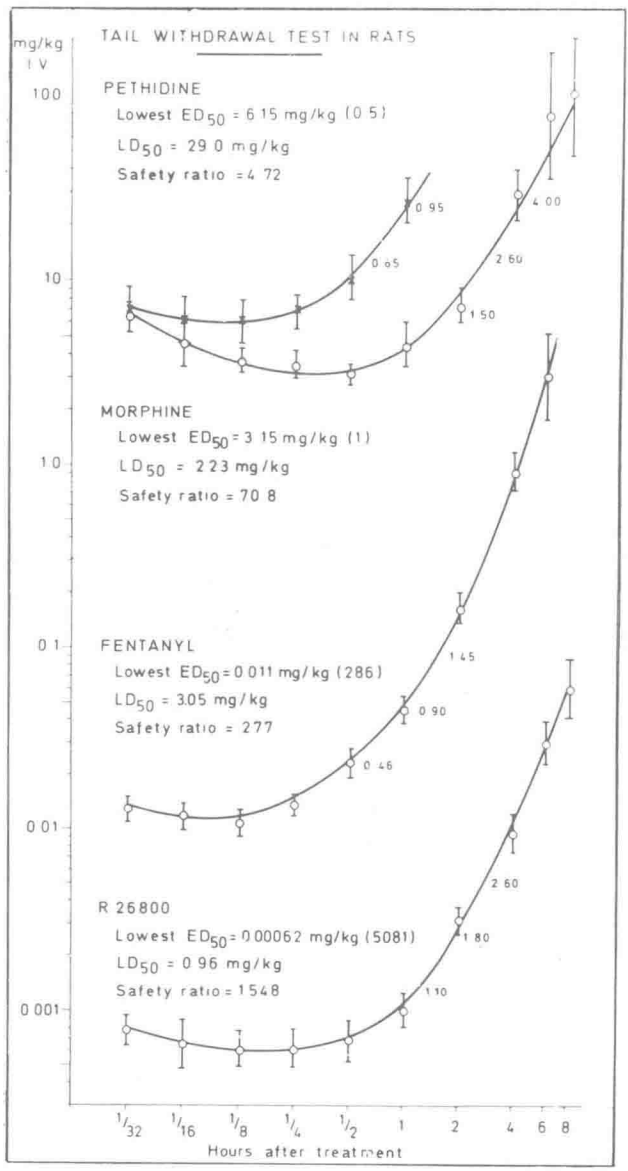


Figure 2. Tail withdrawal test in male Wistar rats ED_{50} for effect > 10 sec after i.v. injection of pethidine, morphine, fentanyl and R26800 against time.

results in higher concentrations of the drug at the receptor sites with the consequence that the potency of the drug is increased. Fentanyl is 286 times more potent than morphine in animal experiments.

The analgesic potency of the drug is measured by the tail withdrawal reaction test in rats, as described by Janssen *et al.* (1963). When the tail of a naive rat is immersed in water at 55°C, the rat withdraws its tail within 6 sec. A drug is considered to have a moderate effect when the tail withdrawal time is more than 6 sec but less than 10 sec and a pronounced effect when there is no tail withdrawal response within 10 sec.

In Fig. 2, the ED_{50} necessary to evoke a pronounced analgesic effect after i.v. administration of pethidine, morphine, fentanyl and R26800, a very potent fentanyl derivative, is plotted against time. From the data, it is concluded that fentanyl is much more potent than morphine and pethidine and that fentanyl has a shorter duration of action, because the slope of the curve is much steeper than that of the morphine and pethidine curves. The safety ratio for fentanyl appears to be larger (277) than that of either morphine (70·8) or pethidine (4·7). When given orally, in the dosage range 0·11–1·62 mg/kg in the same test, fentanyl is about ten times less potent than when administered intravenously (Janssen *et al.*, 1963; Fig. 3).

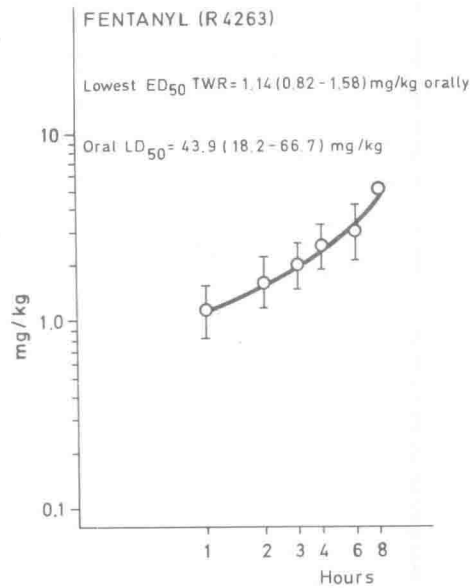


Figure 3. Tail withdrawal test in male Wistar rats ED_{50} for effect > 10 sec after oral administration of fentanyl against time.

To explain the unexpectedly prolonged duration of action of fentanyl in patients in comparison to rats, some authors suggest that fentanyl (by analogy with pethidine) is sequestered in the stomach during operation and is reabsorbed after passage into the small intestine. This seems unlikely to be correct since the doses used clinically are low; only a part of the administered fentanyl finds its way into the stomach; the drug, after absorption from the small intestine, has to pass through the liver where it is metabolized to a certain extent before it reaches the central nervous system and the oral potency of fentanyl is low.

In animal experiments using tritium-labelled fentanyl administered i.v. to male Wistar rats (0·31 mg/kg) it was shown that the compound was very rapidly metabol-

ized and excreted. Most of the drug, plus its metabolites, were excreted within 24 h and the excretion appeared approximately equally distributed between the urine and the faeces (Fig. 4). About 25% of the fentanyl was excreted unchanged, mainly in the faeces.

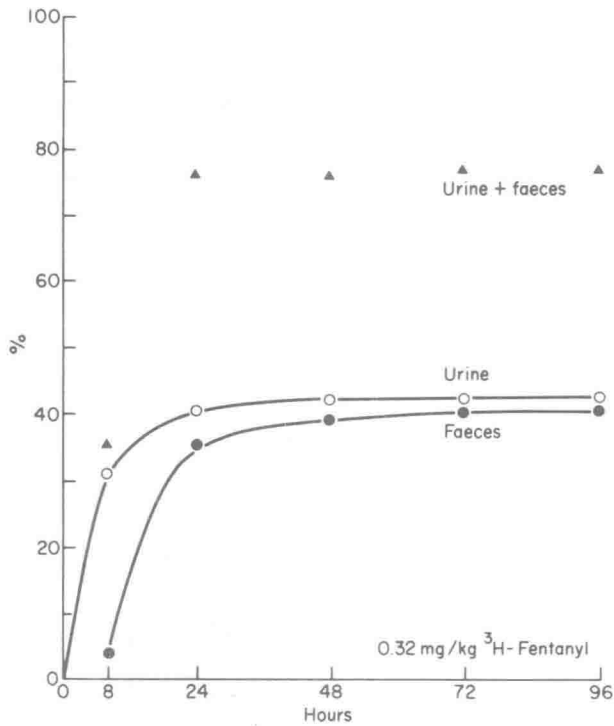


Figure 4. Percentage of administered radioactivity excreted with the urine and faeces in male Wistar rats after i.v. injection of tritium-labelled fentanyl (0·31 mg/kg) against time.

The major metabolic pathway appeared to be oxidative *N*-dealkylation (Fig. 5) resulting in the formation of phenylacetic acid, which is also an intermediate in the catabolism of phenylalanine and a basic metabolite, which itself is devoid of analgesic properties.

Another possible metabolic pathway was found by Maruyama and Hosoya (1969) who administered very high doses (3·5 mg/kg) of unlabelled fentanyl s.c. to female rats and detected another basic metabolite (Fig. 6) which is also pharmacologically inactive. It may well be that this product is only formed when the oxidative *N*-dealkylation pathway is saturated. There is ample experimental evidence that the liver is the main organ for the biotransformation of fentanyl.

Fentanyl is also extensively and rapidly metabolized in man, but apart from the fact that the metabolites are very water soluble, nothing is known about their chemical structure. It is well known, however, that oxidative *N*-dealkylation is a usual pathway for the biotransformation of drugs in man also.

The pharmacokinetics of tritium-labelled fentanyl were studied in the Wistar rat after i.v. injection of 0·31 mg/kg. Within 15 min a peak concentration was reached

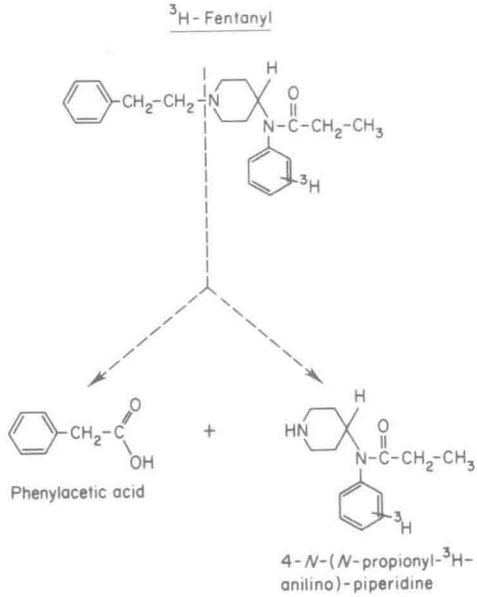


Figure 5. Oxidative N-dealkylation of fentanyl.

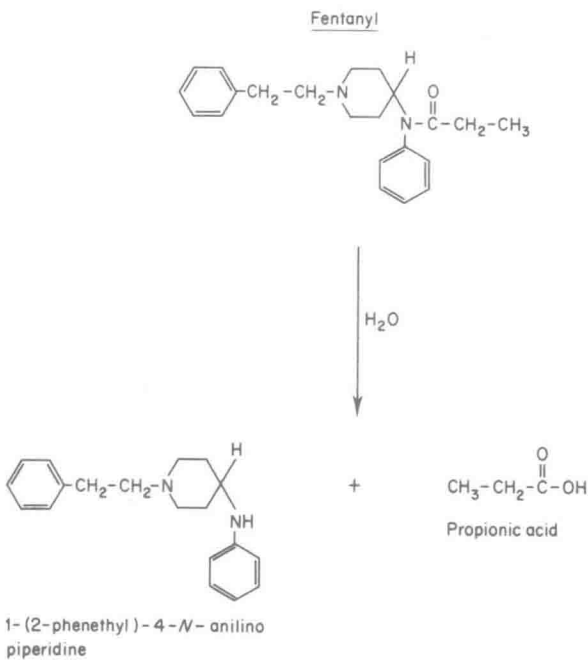


Figure 6. Alternative pathway of the biodegradation of fentanyl.

in the brain and liver. Up to 30 min after the injection, more than 95% of the radioactivity of the brain and blood was due to fentanyl itself, but 15 min after injection, substantial amounts of metabolites were already present in the liver, indicating a rapid biodegradation of the drug in rats. Half an hour after the injection, the elimination of fentanyl starts in the liver, brain and blood. The slopes of the elimination part of the curves are virtually parallel, indicating an identical half-life of fentanyl in the organs under observation (Fig. 7). There is a rapid rise in metabolite concentration

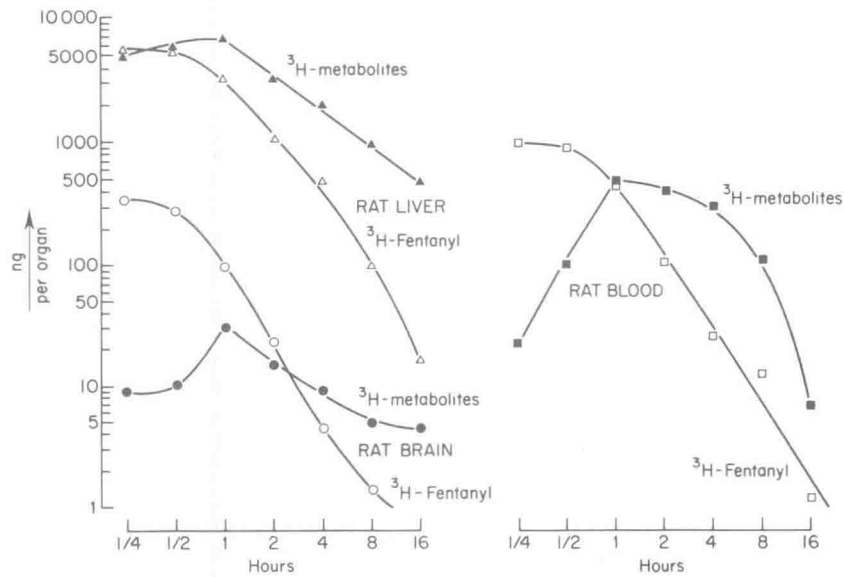


Figure 7. Pharmacokinetics of fentanyl (0·31 mg/kg, i.v.) and its radioactive metabolites in the male Wistar rat.

in the brain and in the blood in the first 60 min. Thereafter, the metabolites are eliminated from the organs at a slower rate than the elimination rate of fentanyl.

Hess *et al.* (1971) found that in rabbits, fentanyl is rapidly eliminated from the plasma after i.v. injection. Within 5 min, 99% of the administered dose had already disappeared from the plasma. At 0·5 min, 24% of the dose was found in the lung, while at the same time the highest brain concentration was reached, about 1% of the dose. The lung has a depot function for the redistribution of fentanyl for about 5–10 min after administration of the drug.

The paucity of publications on the pharmacokinetics of fentanyl in man is understandable, because labelled fentanyl is required, which precludes research on a large number of subjects. However, with the development of a sensitive and specific radioimmunoassay for fentanyl (Henderson *et al.*, 1975; Michiels *et al.*, 1977) this situation will certainly improve and more reports will probably appear in the near future. The data published so far show a triphasic disappearance of fentanyl from serum or plasma. The initial phase is very rapid with a half-life of about 2 min. The drug is taken up by organs with a large blood supply, e.g. lung, kidney, heart and brain. The next phase is one of redistribution and the plasma half-life of fentanyl is about 10 min, the redistribution from lung, kidney and heart being more important than from the brain. The last phase is that of metabolism and excretion with a half-life of plasma fentanyl of about 172 min (Fig. 8). The above mentioned kinetics do not appear to depend on dose. Michiels and co-workers showed that in healthy volunteers the plasma level of fentanyl 2 min after an i.v. bolus injection of 0·2 mg was only

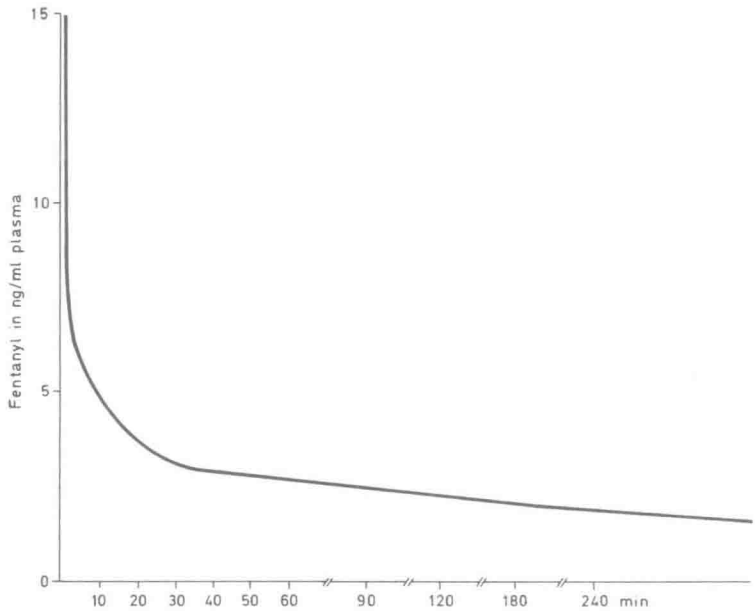
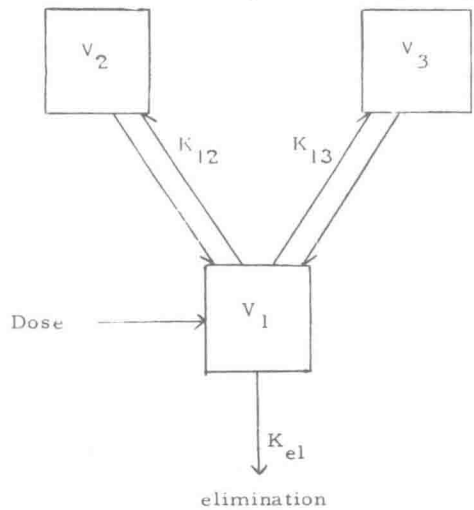


Figure 8. Model curve of the plasma fentanyl concentration against time.

2 ng/ml, 95% of the administered dose being taken up by the tissues, while 6 h after the administration, the plasma level was about 0·2 ng/ml.

Mathematically, the pharmacokinetics of fentanyl in man are best described by a three compartment open model, in which V_1 is a central (e.g. plasma+extracullular water) compartment, V_2 and V_3 are peripheral (tissue) compartments and K_{12} and K_{13} are intercompartmental rate constants. The parameters can be estimated by the method of Hull and McLeod (1976).

Bower *et al.* (1976) showed that there is a large variability in the compartmental volumes and rate constants which is not related to body mass or surface area when fentanyl was administered to eight healthy volunteers (0·2 mg i.v.).



$V_1 = 59{\cdot}5 \pm 46{\cdot}1$; $V_2 = 71{\cdot}7 \pm 61{\cdot}2$; $V_3 = 189{\cdot}4 \pm 97{\cdot}6$ litres;
$K_{12} = 3{\cdot}9 \pm 3{\cdot}8$; $K_{13} = 2{\cdot}12 \pm 0{\cdot}9\ h^{-1}$

Figure 9. Three compartment pharmacokinetic models for fentanyl.