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THE METABOLITES OF FENTANYL AND
ITS DERIVATIVES
PART II

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RESEARCH AND TECHNOLOGY DIRECTORATE

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13. ABSTRACT (Maximum 200 words)

A review of the recent literature has found new studies on the products biotransformation of fentanyl derivatives. Predictions of metabolic pathways have been used to design new drugs.

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PREFACE

The work described in this report was authorized under Project No. 1C161102A71A, Research in CW/CB Defense. This work was started in September 1988 and completed in December 1991.

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THE METABOLITES OF FENTANYL AND ITS DERIVATIVES

PART II

1. INTRODUCTION

The analgesic potency of opium, obtained by air-drying the sap of unripe seed capsules of *Papaver somniferum*, has been recognized for at least three millenia. In 1806, Sertürner isolated morphine, the most pharmacologically active component of opium. While it was recognized for some time that the structure of this alkaloid was not simple, the true dimensions of its complexity were not fully appreciated until its structure was unambiguously assigned by Gates and Tscudi.¹ Morphine is pentacyclic and has five centers of chirality, making its synthesis formidable. Remarkably, Rice² has recently achieved the total synthesis of natural morphine from commercially available 3-methoxyphenethylamine in 20 - 25% yield.

Prior to this discovery, considerable attention was directed toward molecules that preserved those critical structural features of the morphine molecule necessary for analgesic activity but which were considerably simpler to synthesize. The discovery that meperidine³ (methyl 1-methyl-4-phenylpiperidine-4-carboxylate) had about one half the analgesic potency of morphine was an important, if accidental,^{4,5} step in this direction.

It is known that morphine and opioids produce their analgesic effect by interaction with the μ -receptor⁶. In addition to analgesia, these drugs all have associated side effects such as respiratory depression, cardiac depression and dependence. An approach to lowering side effects below unacceptable levels is to use chemical synthesis to discover molecules of such potency that they could be administered at concentrations high enough for effective binding to the μ -receptors, but too low for participation in those interactions that mediate side effects. Partial confirmation of this hypothesis was obtained with the landmark discovery of fentanyl (N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-propanamide) in the 1960's by P.A.J. Janssen.⁷ It was found to have an estimated potency of 50 times that of morphine in humans, yet minimal effect on cardiovascular function. Carfentanil, the 4-carbomethoxy derivative of fentanyl, has a

potency of 27 times that of fentanyl in animal studies.⁷ Sufentanil⁸ and alfentanil⁸ have proven to be useful clinically due to their unique blends of potency and duration of action.

Many factors determine the potency of a drug. A study of the metabolites of fentanyl and its derivatives is of interest for a number of reasons. First, the metabolites may have μ -agonist or -antagonist activity. In this context it is noteworthy that a recent review¹⁰ of the pharmacokinetics of the prototypical μ -agonist, morphine, cites findings that two metabolites, normorphine and morphine-6-gluconuride, are active, the latter being considerably more active than the parent drug. Second, metabolites may contribute to toxicity and other side effects. Third, one may be able to orchestrate the mode of action of a drug by blocking a metabolically labile position. This strategy becomes more attractive as new piperidones, synthetic precursors to the fentanyl family of compounds, become available.¹¹ Fourth, metabolites may serve as useful lead compounds in the synthesis of new fentanyl derivatives. Finally, analysis for metabolites can be useful in confirming prior administration of an opioid. In this review, only phase I biotransformation reactions have been considered. In the previous study,¹² the literature was reviewed through August 1987. This report is a supplement to that report and covers the literature through August 1991.

2. DISCUSSION

Biotransformation of a drug depends on the method by which it is introduced into the body. Available modes include intravenous, intraarterial, intramuscular, subcutaneous, intradermal, percutaneous, inhalation, sublingual, oral and rectal administration.¹³ The mode of administration determines the sequence of organs traversed by the drug on its way to its receptor sites or metabolizing organs. Intramuscular injection, for example, results in 100% of the drug passing through the lung before entering general circulation and exposure to other metabolizing organs such as the liver. A tabulation of first- and second-pass organs is available.¹⁴

Following administration, a drug must be absorbed into bodily fluids and organs across biological membranes.¹⁵ There are passive and active modes for absorption in addition to an

engulfment process known as pinocytosis. The rate of absorption depends on the form of dosage, solubility, blood flow, and diffusion. Once the drug enters the circulatory system, reversible binding to plasma proteins often takes place, facilitating transport throughout the body. In most cases, distribution of a drug can be approximated using a two compartment model consisting of a central compartment where perfusion is rapid (blood, liver, heart, lungs and kidneys), and a peripheral compartment where equilibration with the blood is considerably slower (fat, skin and muscle.)

For the opioids, passage across the blood brain barrier (BBB) is critical if the drug is to interact with central nervous system (CNS) receptors. Clusters of μ -receptors are found in the hypothalamus, thalamus and substantia nigra of the spinal cord.^{16,17} Capillaries carrying cerebrospinal fluid are enveloped by glial cells which are permeable to lipophilic but not lipophobic substances. One reason given for the short onset of action of fentanyl relative to morphine is the much lower polarity of the former. Exit from the CNS apparently takes place at about the same rate for all substances and occurs via a different mechanism, possibly arachnoid villi filtration.¹³

Biotransformation usually occurs in the liver primarily, although the lung¹⁸ and even the brain¹⁹ are possible metabolic sites.^{20,21} Finally, the drug or its metabolites are excreted by means of the renal route if they (or their conjugates) are sufficiently hydrophilic, or by the biliary route, if the molecular weight is high.

Typically the *in vivo* metabolites of a drug are identified by their presence in urine and feces. Sensitive analytical techniques are available to detect the parent drugs and their metabolites.²² It is extremely difficult, however, to evaluate the pharmacological effect of a metabolic product of an active drug. The products found in the excreta, however, may not reflect the molecular environment from which agonists and antagonists are selected by the receptor. Due to factors cited above, the concentration of a metabolite at the receptor and in the excreta might be quite different. In addition, chemical species which do not survive until they are excreted would be undetected. Conversely, no information is obtained concerning the effect of a metabolite at CNS receptors if the mode of administration and the resulting absorption, distribution and elimination do not permit significant passage across the BBB.

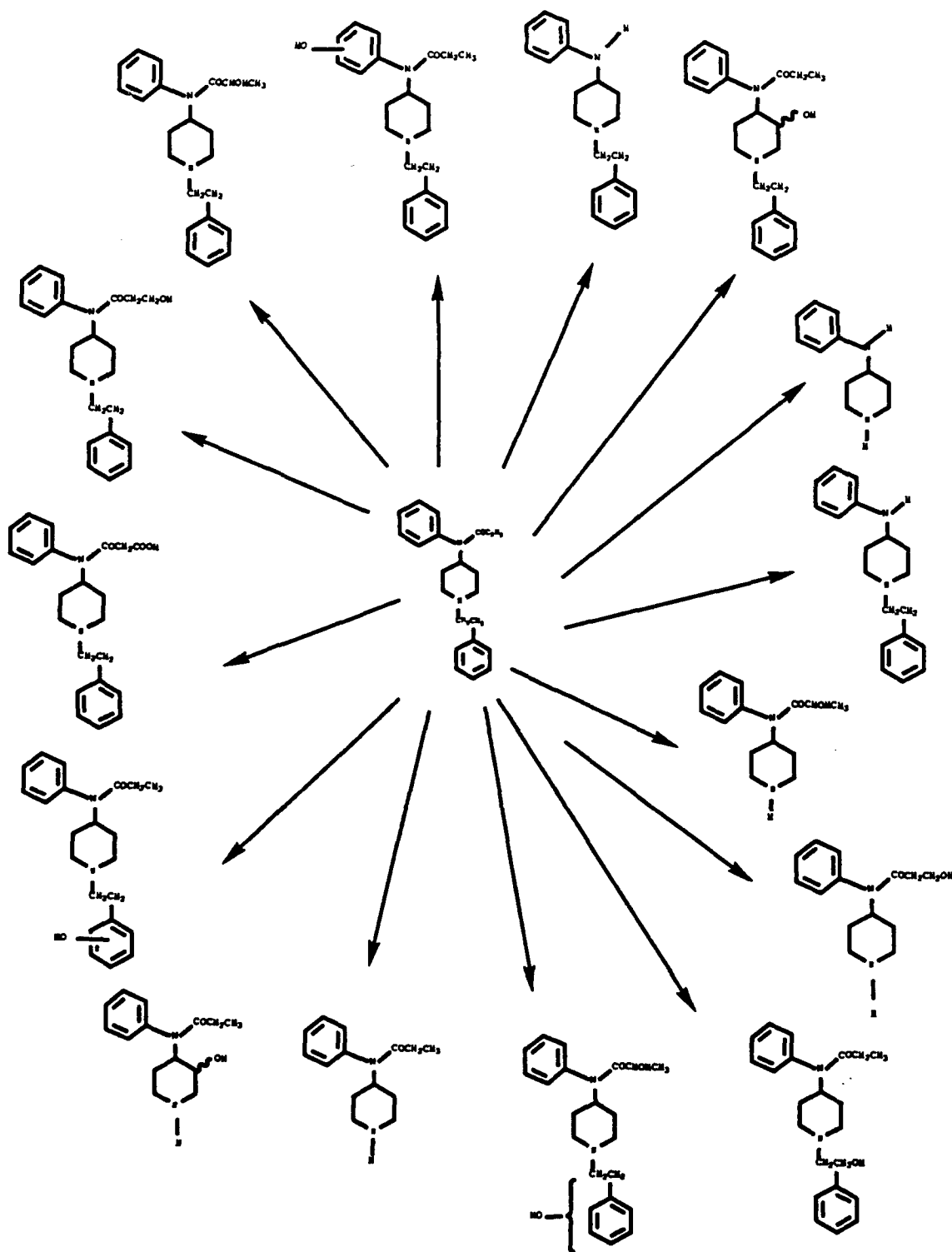
In vitro metabolites have been identified following treatment of the drug with liver microsomes. The liver is assumed to be the principal metabolic site, or representative of biotransformation processes in general. These studies are quite useful, due to the simplified experimental procedure relative to *in vivo* studies, and especially in determining the biotransformation routes for humans where lengthy clinical protocols are avoided.

The known mammalian metabolites of fentanyl are summarized in Scheme 1. Fentanyl metabolites resulting from N-dealkylation at the piperidine nitrogen, hydrolysis of the amide function and hydroxylation at the o- and m-positions of the phenylethyl ring have all been found to be inactive. The activity of the 3-hydroxy metabolites is not known at present, although *cis*-N-(2-fluorophenyl)-N-[1-(2-phenylethyl)-3-hydroxy-4-piperidinyl]propanamide, a presumed metabolite of the corresponding fluoro derivative of fentanyl has 3% the analgesic potency of fentanyl in the mouse hot plate test (MHP).²³ While the stereochemistry of the 3-hydroxy metabolite(s) of fentanyl has not been established, a racemic derivative of one of the possible diastereomers, *cis*-3-methoxyfentanyl has been found to have a potency of 28 times that of fentanyl (MHP.)²³

In the course of his studies of structure activity relations for fentanyl derivatives, Casy²⁴ found that 4-(4-nitrophenylamino)-1-(2-phenylethyl)piperidine, a probable metabolite of the synthetically elusive nitrofentanyl derivative, had an analgesic potency comparable to that of morphine. This is the only known deacylated fentanyl which has shown analgesic activity.

An extensive study of the metabolites of alfentanil and sufentanil in rats and dogs has been published.²⁴ The metabolites were characterized from the urine and feces following intravenous administration of the drugs specifically labelled with tritium at the 3-position of the phenyl ring. Following workup, samples were separated by either high performance liquid chromatography or gas liquid chromatography, and identified by mass spectrometry. The results are presented in Scheme 2. Little parent drug was detected in the excreta, demonstrating that that drugs are extensively metabolized. The primary metabolic routes are N-dealkylation at the piperidine and anilide nitrogens, forming 2 and 6 (after para hydroxylation of the aromatic ring), respectively, and O-demethylation, producing 3. The

Scheme 1



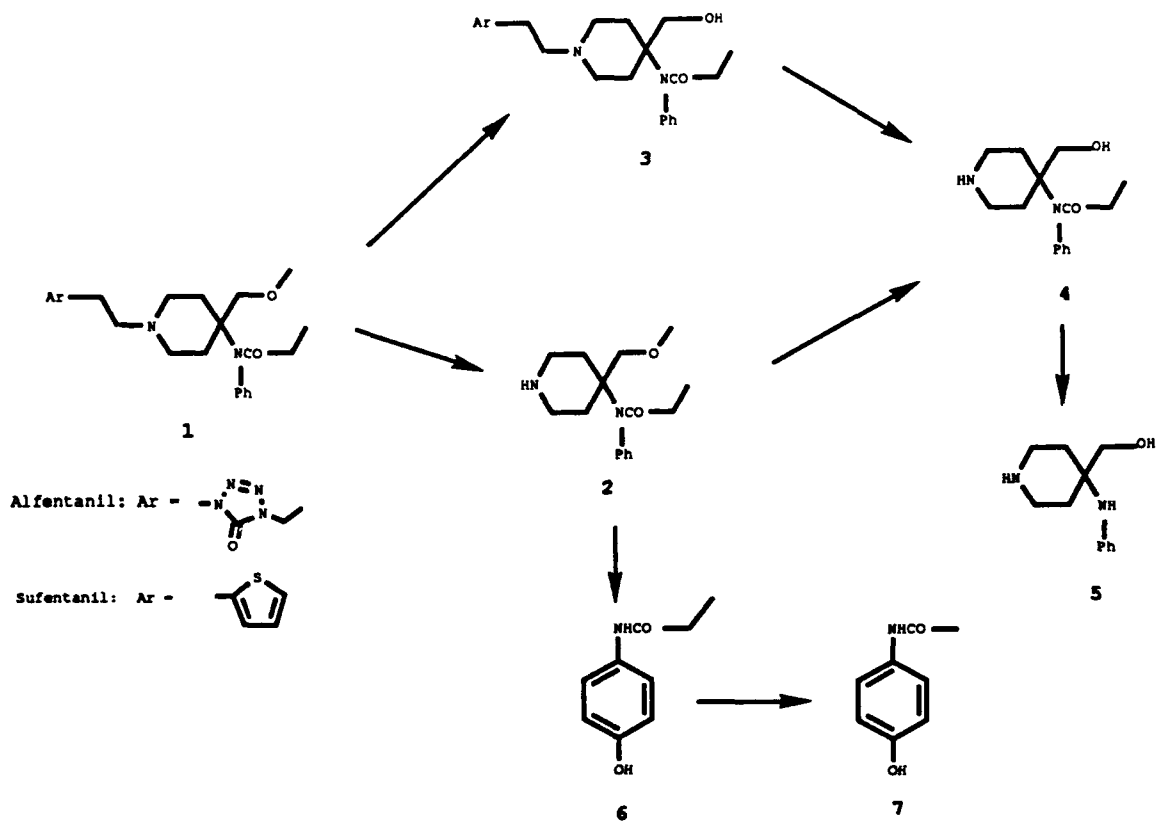
formation of 6 has not been reported for fentanyl, possibly because the other biotransformations are rapid relative to this route. It is noteworthy that further biotransformation along this route via hydrolysis of the anilide and N-acetylation produced acetaminophen, 7, a common, over-the-counter pain reliever. (It should be noted that the quantities of 7 produced are a small fraction of the therapeutic dose, and the mechanism of action is different than that of opioids.) Unlike fentanyl, products resulting from oxidation of the piperidine ring or the propionyl groups could not be detected.

Using dog and rat hepatocytes, extensive cytochrome P-450-dependent metabolism was observed for alfentanil.²⁶ Oxidative demethylation at the piperidine nitrogen and the O-methyl group were the major metabolic routes. Metabolic routes for human, dog and rat liver microsomes were quite similar for sufentanil.²⁷ The results for these *in vitro* studies compared favorably with the *in vivo* results. The principal pathways were N-dealkylation (N-phenylpropanamide could be characterized), O-demethylation and aromatic hydroxylation.

Alfentanil metabolism has been studied using human subjects.^{28,29} Tritium-labelled alfentanil was administered intravenously, and identification of the urinary products was accomplished as described above. N-dealkylation, producing 2, was the main metabolic pathway, followed by dealkylation at the anilide nitrogen, producing 3, which was largely conjugated in the form of its gluconuride. Other metabolites were 3 and 7.

(+)-cis-3-Methylfentanyl has an analgesic potency of 19 times that of fentanyl in studies with rats. No systematic study of the metabolic fate of this compound has been published. A recent study has indirectly established that one route in humans is N-dealkylation at the piperidine nitrogen.³⁰ Since N-dealkylation to produce norfentanils is a major metabolic route for other fentanils, the urine of a patient in a drug treatment center was examined for the presence of 3-methylnorfentanils. A mixture of cis- and trans-3-methylnorfentanyl was detected in the ng/mL range. This mixture, and the fact that norfentanyl was found in the urine sample, probably indicates that the illicit drug sample was impure.

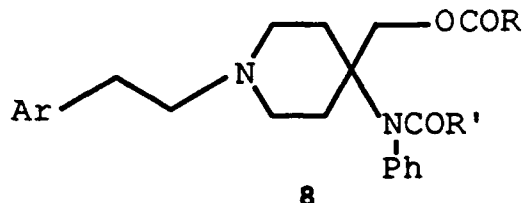
Scheme 2



Brifentanil, *cis*-N-(2-fluorophenyl)-N-[1-(2-(4-ethyl-4,5-dihydro-5-oxotetrazol-1-yl)-ethyl)-3-methyl-4-piperidin-yl]-methoxyacetamide, has been selected for clinical trials for the short surgical procedures typical of outpatient care because of its short duration of action, and high safety ratio in animal studies. Its metabolites in the rat were not characterized, but shown to be more polar than the parent drug by reversed-phase HPLC.³¹

A pharmacological study of ohmefentanyl (2'-hydroxy-*cis*-3-methylfentanyl), an opioid that has a potency of 28 times that of fentanyl, has been published.³² Biotransformation was observed using radiolabeled drug, but the metabolites were not characterized.

Several groups have designed research projects based on presumed biotransformation routes for fentanyl derivatives. Colapret and coworkers³³ synthesized a number of molecules having the general structure 8 (Ar = phenyl, 2-thienyl,



4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl, 2-tetrazol-2-yl or phthalamido, and R = methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, phenyl, methoxy or ethoxy). The hypothesis tested in this study was that the ester and especially the carbonate derivatives would be particularly unstable in the presence of the esterases found in bodily fluids and tissue. Unpublished work in their laboratories established that the corresponding 4-hydroxymethyl compounds possessed little, if any, analgesic activity. It was found, however, that duration of the antinociceptive effect in mice was considerably longer than predicted. Either strong association of the parent drugs with the μ -receptor (confirmed in *in vitro* studies), or poor catalysis of hydrolysis by the esterases were suggested to explain these findings. Implicit in these results is the fact that the rate of uncatalyzed hydrolysis at physiological pH is also low.

Feldman and coworkers³⁴ decided to replace the 2'-phenyl

group of carfentanil with groups that would have similar lipophilicity and steric requirements, but also be subject to the hydrolytic action of blood esterases. Alkyl ester moieties were found to be suitable replacements since they were hydrolyzed by human whole blood to the corresponding carboxylic acid, which was identified as a metabolite, and was approximately 1000 times less potent than the most potent parent drugs. A spectrum of molecules with durations of action ranging from ultrashort to long, depending of the nature of the alkyl group of the ester, have been synthesized.

As part of a program to synthesize new analgesics derived from fentanyl, Bagley and coworkers discovered the first examples of fentanyl-like molecules that display morphine antagonism.^{35,36} In the course of this study, 2- and 3-furoyl-4-amino-1-(2-phenylethyl)piperidine were found to reverse respiratory depression, but not analgesia. This is a significant finding since common antagonists such as naloxone reverse both respiratory depression and analgesia, a potential liability if acute pain accompanies the return of an acceptable respiratory rate during a surgical procedure. The 4-amino compound was inactive. If one makes the reasonable assumption that hydrolysis of the amide functionality is a likely metabolic route, these furoyl compounds are reasonable candidates for short-acting antagonists.

3. CONCLUSIONS

A review of the recent literature has found that new metabolites of fentanyl derivatives have been reported. Known metabolic routes are useful in predicting the types of biotransformations new drugs will undergo. It is hoped that comprehensive studies such as those completed for alfentanil and sufentanil will be published for promising opioid analgesics in the fentanyl family, especially those that exhibit attenuated respiratory depression.

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