THE PROBLEM OF PAIN RELIEF

The problem of pain relief is one that faces every doctor. Indeed as Sir Hugh Cairns (1949) told medical students in an inaugural address at King's College some twenty years ago, "Your patients need from you more than diagnostic and therapeutic efficiency. They do not come to you to be cured; they come to be relieved of their pains and other symptoms, and to be comforted." There can be no doubt that Sir Hugh deliberately specified pain because this symptom more than any other drives the patient to seek his doctor's help. But the difficulties involved in providing such help should not be underestimated.

The oldest and the best known analgesic is opium; for centuries the crushed seeds of the poppy have provided pain relief unsurpassed by any other drug and there are many today who still regard opium, or its purified version morphine, as the best analgesic available. Certainly it is the reference point in the assessment of any new analgesic drug and drugs with an analgesic action like opium are known as "opioids". Morphine relieves pain partly by its influence on mood and this is the cause of the only major drawback to its use, the tendency for patients treated with morphine to develop both a physical and psychic dependence on it. In an attempt to overcome this disadvantage chemists prepared the related compound heroin, and it was some years before it was discovered that this drug had an even greater abuse liability than morphine itself. Many years later the story was repeated when the introduction of pethidine (Demerol) in 1939 led to a marked increase in the number of known drug addicts in many countries.

Drug Addiction.

Like opium, drug addiction has been recognized for hundreds of years but it is only during the present century that its harmful effects both at individual and at public health level have come to be fully appreciated. Unfortunately the response of society has been less concerned with the treatment of addicts than with punitive legislation accompanied by much ill-informed comment. Possibly as a result, the terms "addiction" and "habituation" became so misused that in 1964 the World Health Organization Expert Committee on Addiction Producing Drugs recommended that the terms should be abandoned and replaced by the expression "dependence". For this purpose dependence is defined as a state arising from repeated administration of a drug on a periodic or continuous basis. Its characteristics will vary with the drug involved and the Committee recommend that this should be designated in each instance, for example drug dependence of morphine type.

Drug dependence of morphine type is characterized by: (1) an overpowering desire or need to continue taking the drug and to obtain it by any means; the need can be satisfied by the drug taken initially or by another with morphine-like properties; (2) a tendency to increase the dose owing to the development of tolerance; (3) a psychic dependence on the effects of the drug related to a subjective and individual appreciation of those effects; and (4) a physical dependence of the effects of the drug requiring its presence for maintenance of homeostasis and resulting in a definite characteristic and self-limiting abstinence syndrome when the drug is withdrawn.

The close association between pain relief and changes in mood led many clinicians to believe that pain relief and the development of dependence were inseparable and consequently that no strong analgesic would be found free from abuse liability. Indeed some are on record as stating that the abuse liability was directly proportional to...
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the analgesic potency. Then it was discovered that n-allyl normorphine (nalorphine), a morphine antagonist, possessed analgesic properties of its own (Lasagna and Beecher, 1954). Unfortunately a whole spectrum of unpleasant side effects which included dizziness, sweating, nausea and vomiting (Payne, 1954) made it unsuitable for clinical use, but the observation some time later by Isbell (1956) that nalorphine was virtually devoid of abuse liability stimulated a renewed interest in the possible analgesic properties of other morphine antagonists. In particular a series of compounds, derived from the benzomorphan nucleus was prepared and investigated.

Benzomorphan Derivatives.
Chemically the benzomorphan nucleus is as follows:

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\text{Phenazocine: } R = \text{CH}_3, \quad R' = -\text{CH}_2\text{CH}_3\text{C}_6\text{H}_5 \\
\text{Cyclazocine: } R = \text{CH}_3, \quad R' = -\text{CH}_2\text{CH} - \text{CH}_2 \\
\text{Pentazocine: } R = \text{CH}_3, \quad R' = \text{CH}_2. \text{CH} = \text{C} \quad \text{CH}_3
\]

Of the many derivatives, phenazocine was the first to prove clinically useful. It is a powerful analgesic with little or no sedative effect, presumably because of the ephedrine-like side chain, but unlike other members of the series it has no opioid antagonism and carries the risk of abuse (Houde et al., 1964; Conaghan et al., 1966; Beaver et al., 1968; Hooper, 1969).

PENTAZOCINE
The relative success with cyclazocine encouraged further examination of the benzomorphan derivatives and after preliminary studies had shown that pentazocine was a potent analgesic in man (Keats and Telford, 1964), apparently without the disqualifying side effects encountered with cyclazocine, the extensive clinical trials described in detail in this review were undertaken. The trials confirmed that pentazocine was a powerful analgesic drug and established that the property of analgesia was virtually dissociated from that of dependence. The evidence in support of the claim that its abuse liability was low was sufficiently convincing that in 1966 the W.H.O. Expert Committee on Dependence Producing Drugs was persuaded to release pentazocine from narcotics control.

This does not mean that pentazocine dependence will not occur; virtually every drug in common use has been abused and there is evidence that pentazocine is no exception.

Dependence on Pentazocine.
After three years of general clinical use four instances of pentazocine dependence have recently been reported (Schoolar, Indänpää-Heikälä and Keats, 1969). All the patients were women who had been taking the drug parenterally in doses up to 960 mg daily for up to one year. All had shown a tendency to increase the dosage and all had developed symptoms when withdrawal was
attempted. In hospital, withdrawal produced a syndrome which included sweating, tremors, severe chills, leg and abdominal cramps, nausea, vomiting, itching and rhinorrhoea.

In a subsequent comment (Mungavin, 1969) attention was drawn to the fact that in each instance pentazocine had been taken parenterally and that no case of dependence on oral pentazocine had ever been reported; moreover, all patients had had a previous history of serious drug abuse. Mungavin also emphasized that the pentazocine abstinence syndrome was usually mild and required no more than withdrawal and simple supportive treatment.

Since then dependence on oral pentazocine has been reported in a 21-year-old woman who had been prescribed unspecified narcotic analgesics and who had managed to continue her supply for nearly two years because she enjoyed the subjective effects. Subsequently she switched to oral pentazocine and at the time of admission to hospital was taking up to 200 mg by mouth at 90-minute intervals (Hart, 1969). Although the evidence of pentazocine dependence is definite its occurrence is so rare that it seems unlikely that pentazocine abuse will become a social or public health problem provided that clinicians exercise a reasonable degree of prudence in their prescribing. This impression is confirmed by the W.H.O. Expert Committee (1969) who have just reviewed the position of pentazocine and reaffirmed their earlier opinion that control was unwarranted.

**Analgesic Action.**

The assessment of the analgesic action of a new drug is not easy and many methods have been described involving the use of experimental pain in animals and volunteers. Unfortunately animal tests are difficult to extrapolate to human experience and even when volunteers are used investigators often have difficulty in confirming quantitatively each other’s observations, presumably because of the influence of such factors as experience, training and motivation. Accordingly clinical trials still form the main basis for the assessment of pain relief and pentazocine has been tested in the management of postoperative pain, in patients with chronic pain of malignant origin and in women during labour.

One of the earliest studies of the effect of pentazocine on postoperative pain was that of Keats and Telford (1964) who reported that 10–20 mg/70 kg body weight of pentazocine given intramuscularly produced analgesia equivalent to 10 mg/70 kg body weight of morphine. Lasagna (1965), however, claimed that a dose of 40 mg of pentazocine was needed to equal the analgesic action of 10 mg of morphine in patients with postoperative pain, and Beaver and his colleagues (1966) reported that in patients with pain due to cancer 60 mg of pentazocine were required to obtain the same pain relief as that afforded by 10 mg of morphine.

To some extent these discrepancies were explained when Paddock and his colleagues (1969) in a study involving more than 1000 surgical patients, compared the effects of 5-mg and 10-mg doses of morphine with those of 10-mg, 20-mg and 40-mg doses of pentazocine on both the intensity of the pain and on its duration. They were able to show that when the effects of the analgesics were compared at their peaks, 27 mg of pentazocine gave the same relief as 10 mg of morphine, but when the analgesic potency was assessed over a period of approximately 4 hours the dose of pentazocine had to be increased to 36 mg.

One other factor to be considered in assessing the potency of pentazocine is its isomeric composition. When the dextro and laevo forms were compared with morphine given parenterally to 418 patients with postoperative pain it was observed that 60 mg of dextro-pentazocine was less effective than 5 mg morphine in relieving pain, whereas only 25 mg of the laevo preparation were as effective as 10 mg of morphine (Forrest et al., 1969). In the same study it was noted that other effects like sedation and sweating were also associated with the laevo form.

Pentazocine is effective by mouth; the analgesic effects of orally administered pentazocine were first reported by Kantor and his colleagues (1966) in a study involving 244 patients with moderate or severe postoperative or fracture pain. Pentazocine 50 mg was found to be equivalent in analgesic potency to 60 mg codeine while aspirin 600 mg was superior to a dose of 35 mg of pentazocine. A subsequent study (Beaver et al., 1968) compared the relative analgesic potency of oral and intramuscular pentazocine in patients suffer-
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ing from chronic pain due to cancer. When both intensity and duration were considered, oral pentazocine was one-third as potent as the intramuscular form, but when the peak effect alone was considered oral pentazocine was only one-fourth as effective.

Plasma concentrations of pentazocine correlate well with the onset, duration and intensity of action. By the intramuscular route 45 mg/70 kg gave a mean peak plasma level of 14 μg/100 ml at 45 minutes with a plasma half-life of about 2 hours. Peak analgesia occurred within 1 hour and moderate to good analgesia persisted for up to 2 hours after the peak. After intravenous injection (20 mg/70 kg) peak plasma levels were higher and earlier, but peak analgesia was attained at 15 minutes and lasted about 1 hour. With oral administration peak analgesia was delayed to between 1 and 3 hours (Berkowitz et al., 1969).

According to Beckett, Taylor and Kourounakis (1970) absorption of oral pentazocine is both incomplete and erratic. When an oral dose was given approximately four times greater than an intravenous dose the resultant blood concentrations were only up to twice as great as those achieved after the intravenous injection. The results too were fluctuating plasma levels with secondary and tertiary peaks spread over several hours.

**Pentazocine in Obstetrics.**

Pain relief in obstetrics is a special problem, not only because of the possible action of the analgesic drug on uterine tone and on the progress of labour but also because of the possible effect on the respiratory status of the newborn. In a series of twenty-five patients given pentazocine 45 mg parenterally the intensity frequency and tone of uterine activity was increased as measured by direct intra-amniotic pressure measurements (Filler and Filler, 1966). The progress of labour was slightly accelerated, the foetal heart rate was not affected and no poor Apgar scoring could be attributed to the medication except in one instance in which the mother had been given multiple doses at less than 2-hour intervals. The analgesic effect was regarded as excellent in 18 patients, fair in five and poor in two. The passage of pentazocine across the placenta was investigated by Beckett and Taylor (1967) who compared the blood concentrations of pethidine and pentazocine in both mother and infant at the time of birth. The results, presented as the ratios of cord blood level to maternal blood level of the drugs, varied from 0.4 to 0.7 for pentazocine and 0.7 to 1.3 for pethidine and indicated that pethidine is more rapidly transferred across the placenta than is pentazocine. This observation was confirmed in a double-blind trial of the effects of pentazocine and pethidine in 200 women in labour (Duncan, Ginsburg and Morris, 1969). The same study also showed that pentazocine in labour provides pain relief comparable to pethidine but without significant difference in neonatal respiratory depression. The Apgar score at 1 minute was better in infants of mothers not given analgesic drugs.

**Effect on Respiration.**

Pentazocine shares with other strong analgesic drugs the tendency to depress respiration as mea-

![Respiratory changes with pentazocine 20 mg, morphine 10 mg and phenoperidine 1.5 mg/70 kg.](image)

sured by changes in minute volume, in arterial carbon dioxide tension and in end-tidal carbon dioxide tension, in steady state carbon dioxide responses and in rebreathing carbon dioxide response curves.

Keats and Telford (1964) compared pentazocine 20 mg with morphine 10 mg per 70 kg body weight in eight male subjects and were unable to detect a significant difference in the activity of the two drugs in terms of the displacement of the Va/CO₂ response curve at 1 hour and 3 hours after administration, but the data did suggest that pentazocine had the shorter action of the two drugs. A similar conclusion was suggested by the work of Jennett, Barker and Forrest (1968) who carried out a double-blind comparison between pentazocine 20 mg, phenoperidine 1.5 mg and morphine 10 mg per 70 kg body weight. In this study attempts were made to measure the depression of respiration by the changes in end-tidal Pco₂ during air breathing and in the rebreathing CO₂ response, but because the latter method produced so much variation the authors preferred to rely on the air-breathing end-tidal Pco₂ changes (fig. 1). With the steady state carbon dioxide response as their criterion Dyrberg, Henningsen and Johansen (1967) concluded that in terms of respiratory depression 15 mg pentazocine was equivalent to 50 mg pethidine which gave a ratio of approximately 1:3 on a weight basis. Such a ratio agrees with the analgesic ratio suggested by comparative studies.

Pentazocine has been successfully employed in neuroleptanalgesia in a dose range from 50 to 120 mg in patients undergoing neuroradiological procedures (Brown, 1969; Kay, Keaney and Taylor, 1970), but it is questionable if sufficient pain relief could be obtained for major surgery.

From personal experience when pentazocine was given to patients during halothane anaesthesia the mean arterial carbon dioxide tension increased by 10.8 ± 6.6 mm Hg and the minute ventilation fell to 48 per cent of control, whereas in conscious patients the mean increase was only 6.6 ± 3.5 mm Hg and the minute volume fell to 65 per cent of control. More dramatically, 15 mg pentazocine had the same effect on the carbon dioxide response during anaesthesia as did 30 mg pentazocine in the conscious patient (Potter and Payne, to be published).

This respiratory depression can be significantly reversed by the non-specific analeptic, methylphenidate, 30 mg per 70 kg (Telford and Keats, 1965) and by the potent narcotic antagonist,
naloxone, 8–16 μg per kg intravenously (Kallos and Smith, 1968).

**Cardiovascular Effects.**

Pentazocine differs in its cardiovascular effects from the classical morphine pattern of hypotension and bradycardia. Most investigators have observed a rise in blood pressure accompanied by a slight tachycardia in conscious patients after pentazocine, although Keats and Telford (1964) only encountered hypertensive effects at high dose levels (2 mg/kg) as did Brown (1969). Potter and Payne (to be published) observed a significant increase in mean arterial pressure of 9.5 ± 4.9 mm Hg with a dose of 30 mg given intravenously to adults. The discrepancy is probably related to the method of measurement; the former investigators measured blood pressure indirectly and intermittently whereas Potter and Payne recorded it continuously from a catheter in the radial artery. This hypertensive response is unlikely to be related to hypercarbia since its onset is too rapid and since similar rises have been recorded during controlled ventilation when the carbon dioxide tension was constant (Tammisto, Lahdenuu and Foch, 1967; Potter and Payne, to be published).

Potter and Payne also observed a similar pressor response when pentazocine was given intravenously during anaesthesia with nitrous oxide and with halothane, but in contrast to the effects on conscious patients, the pressor response was preceded by a transient period of hypotension which was accompanied by a slight bradycardia that persisted into the pressor response (fig. 3). The transient hypotension with bradycardia would seem to support the observation of Davie, Scott and Stephen (1970) who reported an early transient fall in cardiac output after pentazocine had been given intravenously to patients anaesthetized with halothane, followed by a return to control values within 10 minutes. Simultaneously a sharp sustained rise in central venous pressure occurred; thereafter a slight rise in mean arterial pressure was noted (fig. 4). In contrast, patients with acute myocardial infarc-
tion treated with pentazocine showed a significant increase in cardiac output together with a persistent rise in central venous pressure of 3 cm \( H_2O \) (Scott and Adgey, 1970). Unlike morphine, which usually causes a fall in mean arterial pressure in patients with myocardial infarction, pentazocine raised the mean pressure and at the same time caused a decrease in the physiological dead-space/tidal volume ratio \((V_d/V_t)\) and a fall in the alveolar-arterial oxygen tension gradient \((P_{A_{O_2}}-P_{A_{O_2}})\) (Lal, Savidge and Chabra, 1969).

Together these observations could be taken as suggestive evidence of a pressor response to pentazocine in the pulmonary circulation and the fact that there is a sustained increase in central venous pressure adds further support to this possibility.

**Unwanted Side Effects.**

The unwanted effects of pentazocine resemble those of other strong analgesics and include nausea, vomiting, drowsiness, dizziness, sweating and rarely euphoria, and headache (Keats and Telford, 1964). Occasionally psychotomimetic reactions with hallucinations and unpleasant dreams have been reported at high dose levels (Hamilton et al., 1967). Hypotension does not occur and severe respiratory depression is unusual even when the drug is given parenterally.

**Use.**

In the United Kingdom pentazocine is prepared in 1- and 2-ml ampoules (30 mg/ml) for injection and in 25-mg tablets for oral use. Caution in administration is needed in patients with severe respiratory distress or with respiratory depression, in patients with head injuries or raised intracranial tension or in convulsive states. Pentazocine is better avoided in the first trimester of pregnancy (Drug Therap. Bull., 1969) and evidence from animals (Rogers and Thornton, 1969) suggests that it should be used with caution in patients receiving mono-amine oxidase inhibitors.

**CONCLUSIONS**

Pentazocine has shown an analgesic potency comparable to morphine and pethidine, with a very much lower abuse liability. It has been used with success in the control of severe pain, in neurolept-
algesia, in postoperative patients, in obstetrics, and in patients with chronic pain of malignancy. Its respiratory effects are also comparable with those of the standard potent analgesics, but it possesses in addition a weak narcotic antagonist activity which remains to be fully investigated clinically. This opioid antagonism is sufficient to provoke withdrawal symptoms in low dose morphine-dependent patients. Parenteral administration in the unanaesthetized subject is associated with a rise in systemic arterial pressure, and an increase in cardiac output resulting mainly from an increased stroke volume. The spectrum of subjective effects resembles that of morphine although the incidence of vomiting may be lower.

From the evidence that has been reviewed it can be concluded that pentazocine is the most promising of the benzomorphan derivatives to reach clinical practice.

**REFERENCES**


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