

commercial preparations are very insensitive. When the first reference preparation is available it would be an advance for a minimum acceptable sensitivity to be established by standards institutions. Such a concept would encourage the preparation of satisfactory commercial preparations.

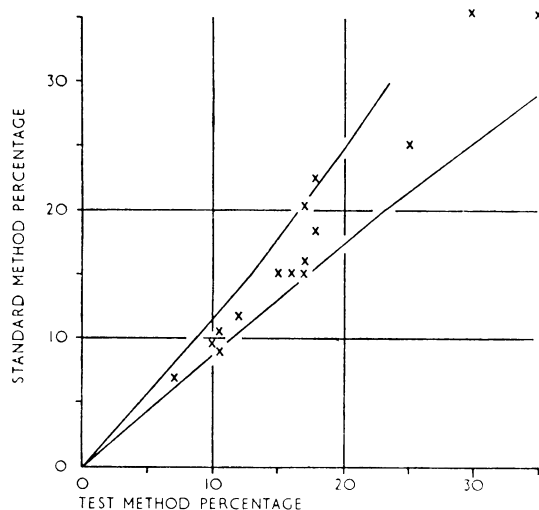


Fig. 7.—Results presented in Fig. 6 converted to percentage activity from appropriate calibration scales and the results plotted against each other. The vertical and horizontal lines give a reasonable "therapeutic range." The limiting lines show the range of error to be expected from the method as a result of simple inaccuracy in determining the clotting-time.

Conclusion

The work done in many centres on the standardization of the one-stage prothrombin time for the control of anticoagulant therapy with coumarin drugs is reaching a stage when it may be possible greatly to improve the general standard of control.

The emphasis on technical care in carrying out the test, always noted by Quick and more recently underlined by Miale, is clearly important. The use of the same technique in a wide

area also obviously has great advantages (Poller, 1964). The introduction of a reference preparation with an internationally recognized scale and a simple method of adjusting various techniques to the scale would round off this work. The calibration scale of commercial preparations could be adjusted to the scale, preparations made individually in clinical laboratories could be similarly calibrated. Moreover, attention to sensitivity to the coumarin defect would undoubtedly improve the reliability of control.

A single scale properly applied at different centres would ensure safety and uniform dosage for a patient moving from one place to another and would greatly improve the standard of clinical trials carried out at more than one centre.

Summary

The control of anticoagulant therapy by the one-stage prothrombin time suffers from the fact that the results of this test are reported differently at different centres. Thus clinical trials with a standard objective of treatment are difficult to organize and a patient cannot travel from one centre to another with any assurance that the level of therapy will remain constant. A method of standardizing the test has been devised so that all may use the same scale of measurement adjusted in each case to fit the preferred thromboplastin. The method is based on the preparation of the standard thromboplastin with which other preparations can be compared.

The work reported in this paper was undertaken jointly on behalf of the M.R.C. Working Party on Anticoagulant Therapy and the International Committee on Haemostasis and Thrombosis.

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Dependence on Dextromoramide

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Dextromoramide (Palfium) has been available as a possible substitute for morphine since 1957. Several accounts presenting evidence of dependence on this drug have been published (Calesnick, 1959; Temple and Attisso, 1961; Flavell Matts, 1962; Thompson, 1964; Johnson and Milner, 1964). The Interdepartmental Committee on Drug Addiction (1961) mentions four cases of addiction to the drug, though it makes no reference to addiction in its Second Report (1965). The W.H.O. Expert Committee on Addiction-producing Drugs (1964) suggested that the term "drug dependence," with a modifying phrase linking it to a particular drug type, should replace the term "drug addiction."

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According to the W.H.O. definition, dextromoramide would fall into the class of drugs producing dependence of the morphine type. The most characteristic feature of this type of dependence is production of the abstinence syndrome within a few hours of administration of the last dose of the drug; the symptoms which occur in this syndrome are described in the W.H.O. report and by Eddy, Halbach, Isbell, and SeEVERS (1965). They can be evaluated by the Himmelsbach (1939) scale. The W.H.O. report states that the abstinence syndrome may also be precipitated in a matter of minutes by the administration of a specific antagonist while continuing to administer the agent responsible for the dependence. Wikler, Fraser, and Isbell (1953) have shown that the administration of nalorphine can act as a specific antagonist to morphine, methadone, and heroin in this way.

The following cases of dextromoramide administration show evidence of dependence of the morphine type as defined by the W.H.O. Expert Committee.

Case Reports

Case 1.—This patient was a married man aged 50 with a short history of heavy drinking only while on active service during the war. In 1957 he was referred to hospital with a history of pain in his right loin, and a small stone was detected in his right ureter, but treatment was not given. When seen in 1958 renal investigations found nothing abnormal. In 1959 he was treated in hospital for intermittent low backache with a lumbosacral belt and heat. In spite of further negative pathological reports from the hospital, his general practitioner prescribed dextromoramide in 1960. In 1962 he was stated to be free of pain, but his general practitioner made a diagnosis of depression and dextromoramide addiction, and arranged for admission to a psychiatric clinic. He was discharged after 11 days with a report that his depression had cleared. In 1963 his general practitioner stated that the dose of dextromoramide had increased from 14 to at least 40 tablets a week, and he was admitted to Moston Hospital for diagnosis and treatment of dependence on dextromoramide.

Case 2.—This patient, a married man aged 45, had a history of intermittent heavy drinking. In 1949 he was admitted to hospital as an emergency case after a fall. He was given 15 mg. of morphine; no severe injuries were found, however, and he was discharged after six days. In 1952 and 1954 he was referred to hospital with a history of intractable and agonizing epigastric pain accompanied by faintness and vomiting. He was treated with alkalis and a milk drip; radiological examination showed only a small deformity of the duodenal cap with some cicatrization but no delay in gastric emptying. A diagnosis of obsessional neurosis was made and medical treatment was recommended. In 1962 he was referred to hospital again with the same symptoms and his doctor reported that the only drug which relieved the pain was dextromoramide. In 1963 he was referred twice to different clinics with a diagnosis of dextromoramide addiction; finally, on admission to Moston Hospital he stated that his dose of dextromoramide had increased to 70 tablets daily during the previous 18 months.

Diagnosis of Dependence

On admission both patients were stabilized on the minimum dose that prevented signs and symptoms of the abstinence syndrome. Case 1 was stabilized on 15 mg.—that is, three tablets six-hourly, and Case 2 on 20 mg. at one-hour intervals. They both became restless and complained of tension during the 15 minutes preceding administration, and complained of abdominal pain, and occasionally vomited if administration of their tablets was delayed for 15 minutes. During the night Case 2 could not sleep for more than two hours without waking up and demanding his dose of dextromoramide.

Confirmation of the diagnosis was obtained in both patients by substitution of dummy tablets for the dextromoramide under double-blind conditions with respect to the doctor in charge of the patients, the nursing staff, and the patients themselves.

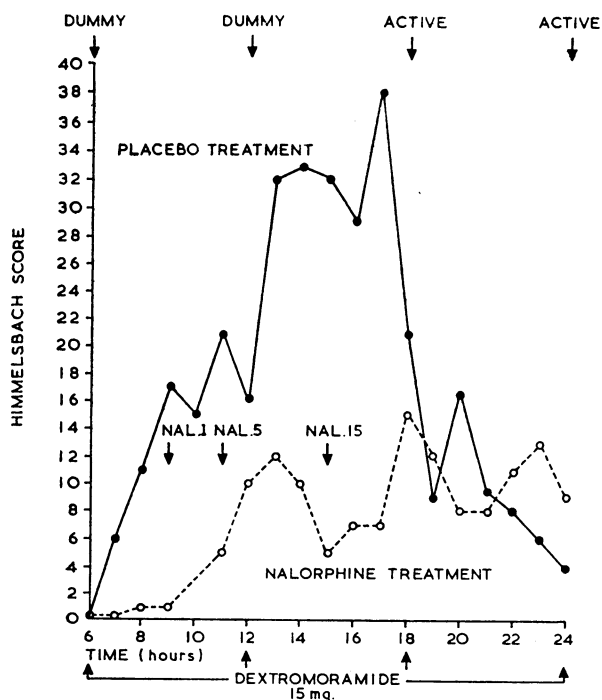
The critical point—that is, the time when the abstinence syndrome reached 50% of its maximum intensity—occurred about 11½ hours after the last dose of dextromoramide in Case 1 (see Chart). The ability of nalorphine to produce the abstinence syndrome was tested in Case 1 after proof of dependence had been obtained with the dummy tablets. Nalorphine was administered three hours after the patient had received his usual dose of dextromoramide. Nalorphine was given successively in increasing doses ranging from 1 mg. subcutaneously up to 15 mg. intravenously. The critical point occurred two and a half hours after administration of the first dose of nalorphine, when the patient had received a total of 6 mg. The nalorphine-abstinence syndrome achieved only half the intensity of that produced by dummy tablets after the patient had received a total of 21 mg. of the drug.

Discussion

These two patients fulfilled all the conditions laid down by the Interdepartmental Committee for addiction to the narcotic drug dextromoramide. According to the definition of the W.H.O. Expert Committee it produces dependence of the morphine type. Evidence that dextromoramide does induce such dependence has been previously reported, but only in those cases recorded by Temple and Attisso (1961) was confirmation of the diagnosis attempted by the use of nalorphine. No evidence has been presented about the degree or duration of the abstinence syndrome which can be induced.

During placebo treatment there was a slight break in the intensity of the syndrome preceding the times when medication was expected. However, when the first patient realized that he had received a dummy tablet at 12.00 hours the syndrome re-appeared with increased intensity. Both patients, and the nurses and doctors, quickly recognized when dummy tablets had been substituted. It is of interest to note that the dummy tablets did not act as placebos to a significant degree in either of these patients. Attention has been drawn to this previously (Wilson, 1965). This finding appears to be characteristic of all drugs which cause dependence of the morphine type. It is also remarkable how the abstinence syndromes produced by dummy tablets and nalorphine differed in their intensity. A large intravenous dose of nalorphine produced an abstinence syndrome having less than half the intensity of that produced by dummy tablets. However, Telford and Keats (1961) have pointed out that the intensity of the abstinence syndrome produced by nalorphine is subject to considerable variation.

Dextromoramide had been administered to both patients in the first instance for the relief of relatively slight and temporary pain; there was little evidence of serious organic disease in either patient. The vague symptoms suggesting the presence of renal, duodenal, or sacro-iliac disease, and its medical and surgical treatment, could in the later stages have been caused by the abstinence syndrome. The fact that both patients had been taking dextromoramide was either not known or mentioned so briefly as to be ignored when the patients were admitted to hospital. Drug dependence of the morphine (Interdepartmental Committee on Drug Addiction, 1965) and amphetamine (Kiloh and Brandon, 1962) types induced as a result of administration



Relative effects of placebo and nalorphine treatment on induction of the abstinence syndrome during dextromoramide dependence. During placebo treatment dummy tablets were substituted for the active tablets of dextromoramide at 6 a.m. and 12 noon. During nalorphine treatment 1 and 5 mg. of nalorphine were administered subcutaneously at 9 and 11 a.m. and 15 mg. intravenously at 3 p.m.

for non-therapeutic reasons is recognized to be of increasing importance among younger people in Britain (Connell, 1964; Bewley, 1965). Dependence on an extensive range of other drugs is also becoming more common (Wilson, 1965; Madden and Wilson, 1966). This alarming increase in non-therapeutically-induced dependence must not be allowed to withdraw attention from the possibility of causing dependence in patients as a result of unwise or ignorant prescription of dependence-producing drugs for therapeutic reasons.

Summary

Two cases showing the features of dependence on dextromoramide are described. Dependence had been produced in both patients after dextromoramide administration for relatively slight and temporary pain. On admission to hospital they were taking dextromoramide in doses of 15 mg. six-hourly and 20 mg. at one-hourly intervals. The diagnosis was confirmed in both cases by production of the abstinence syndrome by substitution of dummy tablets for dextromoramide under double-blind conditions, and in one case by the administration of nalorphine. The abstinence syndrome was more severe, but occurred later, after the administration of the dummy tablets. The possibility that the features of the abstinence syndrome can lead to misdiagnosis is discussed and the importance of recognizing therapeutically induced drug dependence in hospital is stressed.

We should like to express our thanks to Dr. J. S. Madden, consultant psychiatrist in charge of the addiction unit at Moston Hospital, for his interest, and to the nursing staff in the unit for their assistance and co-operation in those investigations. We also wish to thank M.C.P. Pure Drugs Limited for supplying the dummy tablets of dextromoramide which were used in the investigation.

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Preliminary Communications

Immunoradioactive Agent against Cancer

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Cancer-specific antibodies have been produced against both experimental and spontaneous human tumours, but there is little evidence that they have any inhibitory or destructive effect on tumour cells in vivo (*British med. J.*, 1966). In a report of the production of a specific precipitin against renal cancer in a human subject (Nairn *et al.*, 1963) it was suggested that, though not therapeutically effective itself, specific antibody to tumour might localize on the surface of tumour cells and act as a homing carrier for cytotoxic, radiotherapeutic, or chemotherapeutic agents. We have recently developed a successful experimental model of such an effect, using Ehrlich ascites tumour in mice and a specific antitumour serum coupled with ¹³¹I.

METHODS

The experimental tumour and test system were provided by Ehrlich ascites tumour grown in Balb/c mice. Male and female mice about 2 months old were inoculated intraperitoneally with approximately 2.5×10^7 tumour cells in 0.25 ml. of ascitic fluid and physiological salt solution. Use of the ascites tumour has the advantages of avoiding contamination by normal connective-tissue cells of tumour stroma and of permitting free access to tumour cells by any antisera injected into the peritoneal cavity.

ANTITUMOUR SERA, IMMUNOFLOUORESCENCE, AND RADIOACTIVE TRACING

Two adult New Zealand rabbits were immunized by intramuscular injections of 1 ml. of a 25% (w/v) saline suspension of viable Ehrlich ascites tumour cells emulsified with an equal volume of complete Freund's adjuvant, and the inoculation was repeated after six weeks. During the ninth week the rabbits received a further injection of ascites tumour cells without adjuvant, and this was repeated two days later. Thus each rabbit received, in all, four immunizing injections of the same dose of tumour cells, the first two accompanied by adjuvant; both rabbits were bled one week after the last injection. Species-specific and other irrelevant antibodies were removed from the antisera by successive absorptions with homogenates of liver, kidney, and spleen from Balb/c mice.

When tested by gel diffusion both sera before absorption gave two precipitin lines against ascites tumour homogenate and other mouse tissues; there was no sign of any tumour-specific precipitin reaction after serum absorption with nontumour tissue preparations. One serum, used for the majority of experiments, was tested by complement fixation with doubling dilutions of serum against equal volumes of ascites tumour-cell homogenate containing 100 µg./ml. protein nitrogen, using two minimum haemolytic doses of complement. The unabsorbed serum had a titre of 1/32, and after absorptions with mouse, liver, kidney, and spleen homogenates this was reduced to 1/8. Substitution of a tumour-cell preparation for one of these absorptions caused a reduction in titre, possibly complete loss, but this could not be measured exactly because of anti-complementary activity of the absorbed serum; the preimmune serum gave a negative reaction.