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AMIPHENAZOLE AND MORPHINE IN PRODUCTION OF ANALGESIA

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Shaw and Bentley (1952) were the first to point out that a dog completely narcotized with morphine (and sometimes hyoscine) could be restored to normal within a few minutes by an intravenous injection of 2:4-diamino-5-phenylthiazole (amiphenazole; "daptazole," DHA 245). The most interesting part of this phenomenon was the complete restoration of consciousness of the dog. This work has been confirmed (Gershon and Shaw, 1958). It was also shown that the analgesia produced by the morphine was not affected by the amiphenazole.

By means of the use of amiphenazole, large doses of morphine (up to 200 mg. q.i.d.) were given to patients suffering from intractable pain in terminal carcinoma (Shaw and Shulman, 1955; McKeogh and Shaw, 1956).

This use of the combination of morphine and amiphenazole has continued in Melbourne for a period of nearly four years. The same excellent results have been obtained in about 500 patients. The combined drugs have been used by others in a similar manner (Hügin, 1956; Holmes, 1956; Hayward-Butt, 1957; Dundee, 1957; Overton, 1957).

These early results led us to believe that amiphenazole was a morphine antagonist similar in nature to nalorphine, etc., with the exception that the analgesia was not antagonized and that amiphenazole had no side-effects when given alone. Recent work by us (Christie *et al.*, 1958) has led us to modify this view.

It is the purpose of this paper to explain the exact nature of the action of amiphenazole. In a previous paper (Christie *et al.*, 1958) we had shown that amiphenazole had little influence on morphine-induced nausea and vomiting. Cyclizine chloride ("marzine") is the drug of choice here. Amiphenazole has an irregular stimulating action on an already established morphine-induced respiratory depression when given as a single dose. Although Shulman and Trethewie (1956) refer to amiphenazole as a respiratory stimulant, others have noted its unsatisfactory respiratory stimulant action, and on this account have dismissed the drug as being valueless as a morphine antagonist (Bonnycastle and Costa, 1955).

Our approach to the problem has been to obtain objective evidence that amiphenazole does influence the action of morphine. The main approach has been through psychological testing. Unfortunately, the material at our disposal, elderly and failing cancer patients, has not remained in a constant state long enough to enable adequate controls to be used. The difficulty of carrying out such work on healthy volunteers has been stressed earlier (Christie *et al.*, 1958). Although the psychological testing has been of help to us, we have had to rely more on the observations of trained personnel, nursing and medical, and especially the medical specialists in charge of the cases. We would be the first to admit the inadequacy of such evidence, but we are impressed with the unanimity of opinion expressed despite staff changes which occurred over a period of four years. One of the members of the present team is an experienced psychologist.

In all, 27 cases have been assessed for the work. Below are given case histories of 10 patients whose condition and responses permitted the nearest approach to a controlled experiment. The remaining 17 cases showed aspects similar to these, but the results were neither so clear nor so extensive.

Material and Methods

The series consisted of 27 patients with intractable pain of terminal carcinoma. The sexes were about equally represented. No attempt was made to classify the type of malignancy. Similarly, the assessment of pain was on a subjective basis. While this method may be open to objections, nevertheless it was felt that the duration and extent of the pain made the results more reliable than they would be, for instance, in post-operative pain.

Psychological Testing.—As has been mentioned, two major obstacles are encountered in obtaining measures of the behavioural changes which are indicated by clinical observation: (a) patient impaired by illness, and (b) lack of tests known to be sensitive to these changes. Several techniques were attempted, however, and these have provided indications that the effects are measurable and may be better

handled by other techniques being developed at present. The techniques used were (1) Wechsler (1945) memory scale; (2) hand steadiness (Hill and Belleville, 1953); (3) sections of Wechsler adult intelligence scale (Wechsler, 1944)—(a) arithmetic (time score and accuracy), (b) digit span, (c) Koh's block design test (time score and accuracy); (4) spiral after-effect test (Price and Deabler, 1955).

Clinical Assessment Procedure.—The patients were under continual observation by the nursing staff. One of the sisters in charge of one of the wards had occupied this position for four years before the introduction of the combined drug therapy and has continued in the same position for the four years since the beginning of the treatment. The patients were seen at least twice a week by three of the authors (S. G., N. O., F. H. S.). The procedure we endeavoured to follow was to start the patients on morphine, which was given in increasing amounts over the next few days until complete 24-hour analgesia was achieved by injections at six-hourly intervals. When the patient showed a marked drowsiness or narcosis (or respiratory depression) amiphenazale was introduced and the patient kept under observation. At a later date the amiphenazale was withdrawn abruptly and again careful observation was made. When a change had been observed amiphenazale was reintroduced.

Case Reports

Case 1.—Man aged 65. *August 9, 1957*:—Morphine, 65 mg. q.i.d. Lethargic and unable to concentrate but not depressed; well oriented. *August 16*:—Morphine, 100 mg. q.i.d.; amiphenazale, 60, 60, 20, 20 mg. (given with the morphine at six-hourly intervals in the dosages indicated). Much more active conversation, more confident. Reads the paper and takes interest in the news. Well oriented. *September 11*:—Morphine, 100 mg. q.i.d.; amiphenazale, 60, 60, 20, 20 mg. Quite alert and even a little aggressive. *September 24*:—Morphine, 100 mg. q.i.d.; amiphenazale, 20, 20, 0, 0 mg. No interest in anything. Very little contact with events around him. The reason for the reduction in the amiphenazale was the fact that the patient fully appreciated his hopeless state and it was considered more humane to have him partly narcotized. *October 4*:—Morphine, 100 mg. No amiphenazale. Patient narcotized. *October 6*:—Died.

Case 2.—Man aged 20. *July 2, 1957*:—Morphine, 15 mg. q.i.d. Cheerful; reads and draws, but is drowsy most of the time and has some difficulty in focusing. Well oriented. *July 9*:—Morphine, 20 mg. q.i.d. Awakens in semi-dream state. Great difficulty in focusing. Cannot concentrate enough to read and understand, but if pressed can read out words. *July 16*:—Morphine, 20 mg. q.i.d. One day without morphine had been tried, but withdrawal syndrome started, so returned to full dose. Given hand steadiness test; then put on amiphenazale, 60, 60, 40, 20 mg., and morphine, 20 mg. q.i.d. *July 19*:—Claims to be feeling better, but still has some difficulty in concentrating. Hand steadiness test repeated; very significant improvement ($P=0.005$). Remained alert until near death, when amiphenazale was discontinued because awareness of his condition caused distress.

Case 3.—Man aged 55. Patient was a morphine addict of 12 years' standing. He had often tried to stop, but always experienced such a severe withdrawal syndrome that he was afraid to try again unaided. Previous attempts with methadone and corticotrophin had not given freedom from the discomfort. Sudden total withdrawal with amiphenazale (see record below) produced no effect at the time, although later, when the patient was told that he had been taken off on a certain day, he recalled slight symptoms, but so much less than he had ever felt before that he had not really noticed them. *November 23, 1957*:—Morphine, 65 mg. q.i.d. Very lethargic, with slow, slurred speech; not very talkative, but co-operative in tests. Given arithmetic, digit span, Koh's block design test, and spiral after-effect test. *December 3*:—Morphine, 65 mg. q.i.d.; amiphenazale, 50 mg. orally and 10 mg. intramuscularly q.i.d. More active,

and brighter speech. Generally alert and interested in progress. Tests repeated. *December 15*:—Amiphenazale, 20 mg. intramuscularly q.i.d. Morphine abruptly stopped. Has shown no sign of withdrawal syndrome. Is even brighter and more normal than on November 23. Claims to have had his "first good night's sleep." Tests repeated. **Test results**:—Although there are not enough for statistical treatment, the trend is interesting. Arithmetic: time taken decreased by 43% between the first two trials and by another 22% between the second and third trials. Digit span: number remembered increased slightly over the three trials. Blocks: time taken decreased by 19% over first two trials, and the third was the same as the second. Spiral after-effect: time of effect increased from first to second, but decreased from second to third. This latter may have been due to some barbiturate which he had received the evening before testing.

We have treated one other morphine addict (female) in the same manner with the same successful result.

Case 4.—Spinster aged 50. *July 16, 1957*:—Morphine, 15 mg. q.i.d. Feels much more sleepy than usual, but can concentrate on embroidery. Given hand steadiness test. *July 19*:—Morphine, 15 mg. q.i.d.; amiphenazale, 20, 20, 20, 20 mg. Feeling brighter and much less sleepy. Expressed surprise that she was no longer sleeping during the day. Ward staff also commented on this; hand steadiness test repeated and showed improvement which is almost significant ($P=0.07$). Continued on morphine and amiphenazale for two months. Morphine stopped because patient no longer had pain. She remained bright and alert over whole period, with no withdrawal syndrome.

Case 5.—Married woman aged 60. *February 18, 1958*:—Morphine, 100 mg. q.i.d.; amiphenazale 60, 40, 40, 20 mg. This patient has been on the above medication for many months and has been bright, cheerful, and alert throughout. She walks about freely, both in her ward and in the grounds, and reads papers. Clinically, the addition of amiphenazale has made her bright and alert, whereas before its addition she was very drowsy, unable to read, and remained bed-ridden. Clinical condition (gross basal-cell carcinoma involving half the face and palate) precluded valid testing. *April 18*:—Patient on same dose of morphine and amiphenazale, and condition unchanged.

Case 6.—Man aged 70. *October 9 and 14, 1957*:—Morphine, 50 mg. q.i.d. Very depressed and always complaining. On the verge of weeping, and wanting to die. *November 7*:—Morphine, 65 mg. q.i.d.; amiphenazale, 60, 60, 40, 40 mg. Considerably brighter and admits feeling better. *November 19*:—Morphine, 100 mg. q.i.d.; amiphenazale, 100 mg. b.d. Well oriented, but depression returned, although not quite so bad as on November 7. Condition continued thus until *February 10, 1958*:—Morphine, 145 mg.; amiphenazale, 200, 200, 150, 0 mg. Within several days of this amiphenazale increase he was completely changed in his mood and general outlook. He volunteered for the first time that he felt much better and thanked the doctors for what they had done. There was a great change from the previous irritable, dissatisfied attitude, with depression, weeping, and hypochondriasis—being quite cheerful and confident. This condition continued for six weeks. *March 31*:—The patient said he required no more morphine, so it was discontinued abruptly. No withdrawal symptoms appeared. *April 3*:—Complained of pain; morphine, 65 mg. b.d., given with amiphenazale, 200, 200, 150, 0 mg. Pain controlled. *April 10*:—Patient's condition worse. Morphine discontinued; amiphenazale continued. No pain; no withdrawal symptoms. *April 14*:—Patient's condition improved again.

Case 7.—Man aged 57. *November 12, 1957*:—Morphine, 50 mg. q.i.d.; amiphenazale, 40, 40, 20, 10 mg. Had been put on to amiphenazale because he was so sleepy that he could not keep awake for visitors. On amiphenazale he was much wider awake. *November 19*:—Morphine, 50 mg. q.i.d.; no amiphenazale. Feeling sleepy all day and could not talk to visitors; unable to read the paper. *Novem-*

ber 28:—Morphine, 50 mg. q.i.d.; amiphenazole, 20, 100, 100, 10 mg. Brighter, no longer drowsy, and able to converse with visitors and read easily. November 30:—At this point amiphenazole was discontinued and he became drowsy again and unable to stay awake for visitors or to read. December 3:—Restored to amiphenazole, 40, 120, 120, 10 mg., and again became bright. This patient's level of alertness could be altered at will by altering the dose of amiphenazole which accompanied his morphine.

Case 8.—Married woman aged 56. This patient had risen slowly to a dose of morphine, 110 mg. q.i.d., with amiphenazole, 40, 40, 20, 20 mg. She was taken off amiphenazole; after 10 days on this dosage of morphine alone, she appeared normal except for slight nausea and tremor. However, further questioning and administration of the Wechsler memory scale showed gross confusion and disorientation of a type typical of a brain lesion or toxic psychosis. She was incapable of performing any task properly. She was given amiphenazole, 60, 60, 40, 40 mg., and over a week she recovered until she became indistinguishable from a normal person. Her Wechsler memory scale corrected score rose from 66 to 98 over that week. It was thought unethical to repeat withdrawal of amiphenazole. This patient has continued medication with morphine and amiphenazole until the time of writing (May, 1958), and at no time has there been a recurrence of an episode similar to that when taken off amiphenazole.

Case 9.—Married woman aged 55. For some weeks this patient was maintained successfully on morphine, 15 mg. q.i.d., with amiphenazole, 50 mg. q.i.d. The patient's liver became enlarged and jaundice appeared, soon after which there was a sudden onset of drowsiness. Amiphenazole was increased from 100 mg. to 150 mg. to 200 mg. q.i.d. with no effect. Respirations dropped to 6 a minute. Death occurred one week after the onset of the drowsiness. At necropsy the liver weighed 2,800 g. and showed almost complete replacement by growth.

Case 10.—Man aged 60. For some weeks maintained successfully on morphine, 15 mg. q.i.d., with amiphenazole, 80 mg. q.i.d. A sudden onset of drowsiness coincided with a very tender enlarging liver. Morphine was discontinued except occasionally at night, but amiphenazole continued. No improvement occurred and the liver continued to enlarge. Death occurred just under one week after the onset of drowsiness. At necropsy the liver weighed 2,150 g. and showed diffuse nodular secondaries.

Up to date, five cases which closely follow the pattern of Cases 9 and 10 have been observed. In the latter cases, after the enlargement of the liver the onset of drowsiness could be predicted in each case, and this was not controlled by an increase in the amiphenazole dosage.

Discussion

The 10 case histories given are illustrative of the results which have been obtained with 500 patients over a period of four years. The following points can be made with a considerable degree of certainty.

In the presence of amiphenazole: (a) Morphine may be given in large doses (200 mg. q.i.d.) without any risk to the patient, provided the usual small doses are given at first. The dosage can be increased rapidly over a few days. (b) Drowsiness does not develop unless there is gross liver damage. The degree of alertness of the patient can be controlled by varying the dose of amiphenazole. (c) Addiction to morphine does not develop. This can be stated for the following reasons: (1) euphoria is absent, (2) no patient has ever expressed a craving, and (3) in at least four cases in which morphine (over 65 mg. q.i.d.) has been given for months there were no withdrawal symptoms on abrupt cessation of morphine administration. (d) Complete analgesia for 24 hours in the day can be obtained. The psychological value of the patient's never experiencing pain cannot be stressed too much. (e) It is necessary to reduce the dose of amiphenazole at night, otherwise the patient will complain of insomnia. (f) In certain cases, where the patient

becomes aware of the hopelessness of his condition and when the downhill progress is rapid, it is necessary to omit the amiphenazole.

The mechanism of the combined role of morphine and amiphenazole is still unknown. A tentative hypothesis is that morphine and amiphenazole combine, probably in the liver, to form a non-narcotic analgesic substance. The evidence for this is that (1) the beneficial effect of the addition of amiphenazole to a drowsy patient already receiving morphine usually takes several hours to become apparent—for example, amiphenazole has only limited value in controlling the respiratory depression and vomiting induced by single doses of morphine (Christie *et al.*, 1958); (2) patients with liver damage do not derive benefit from amiphenazole; (3) patients suddenly deprived of morphine do not show withdrawal symptoms—that is, they are not really deprived of morphine but of the new compound (morphine and amiphenazole), and this deprivation does not lead to withdrawal symptoms; and (4) a similar suggestion would explain the lack of addiction.

This hypothesis, if correct, would indicate the method to be employed in the post-operative use of morphine and amiphenazole. About two days before the operation several small doses of morphine and amiphenazole should be given. Then immediately in the post-operative period the dose of morphine (with amiphenazole) could be increased to the desired degree to produce complete analgesia for intervals of six to eight hours as long as the pain continues (see Weber, 1958).

It should be particularly noted that the doses of amiphenazole used at present are much greater than those previously recommended. As much as 200 mg. may be given t.i.d. or q.i.d., either orally or intramuscularly.

More recently (Gershon *et al.*, unpublished) it has been shown that large doses of amiphenazole (up to 200 mg. a day) will relieve mild depressive states. This action would offer another explanation for the anti-narcotic effect of amiphenazole.

Summary

The beneficial effect of amiphenazole in preventing drowsiness or narcosis when large doses of morphine are administered in intractable pain of terminal carcinoma has been confirmed.

Addiction does not develop, so that the morphine may be withdrawn at any time without the production of withdrawal symptoms.

Case histories supporting the above conclusions are presented.

A tentative hypothesis for the mode of action of amiphenazole is advanced.

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