INTRATHECAL ISONIAZID IN TUBERCULOUS MENINGITIS

BY

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The demonstration that isoniazid is inhibitory to the tubercle bacillus (Robitcek, Selikoff and Ornstein, 1951) and possesses potential advantages in the treatment of tuberculous meningitis on account of the freedom with which it diffuses into the cerebrospinal fluid (Fletcher, 1953) has led to its widespread and successful use in this disease. The readiness with which C.S.F. concentrations can be maintained after oral administration has permitted a great reduction in the duration and frequency of intrathecal streptomycin therapy.

Numerous series have now been reported in which results compare favourably with those in which streptomycin alone or in combination with antibiotics other than isoniazid have been used. In several, reliance has been placed on systemic therapy by isoniazid and streptomycin while intrathecal therapy has been virtually withheld (Anderson, Kerr and Landsman, 1953; Bulkeley, 1953; Smellie, 1954; Fitzpatrick, 1954. With such régimes the recovery rates have been higher than any achieved previously without isoniazid so that physicians have shown a justifiable inclination in this country and in America to dispense with intrathecal injections. It is nevertheless realized that to do so in all cases would be therapeutically unsound (Lorber, 1954), and it must be borne in mind that often in these series a short course of intrathecal therapy had been given in the critical early stages. The improved recovery rate has doubtless been assisted by the larger proportion of cases now admitted for treatment at an early stage of the illness. There remain those in which for one reason or another the diagnosis is established only when the disease has reached an advanced stage, and from the nature and variety of the symptoms it is probable that such cases will continue to be seen. Although this group is small it still carries a high mortality rate and incidence of neurological complications, and reveals the limitations of chemotherapy. This study of isoniazid administered intrathecally was undertaken to determine whether any advantages might be gained by intrathecal administration, since the antibiotic's efficiency in vivo in respect of bacteriocidal power and ability to penetrate ischaemic tissues depends upon its concentration.

Torres-Gost (1953) has reported encouraging results with this form of treatment but he gives no details of the toxic or side-effects encountered. The present report is concerned primarily with this aspect of intrathecally injected isoniazid and forms a preliminary report on its therapeutic value.

Régime of Treatment

Streptomycin. Streptomycin (20 mg. per lb. of body weight daily) is injected intramuscularly once daily, and, when the infection has been partially controlled, on alternate days. The duration of treatment varies from three to four months or until high frequency deafness is first detectable audiographically.

Streptomycin is injected intrathecally through the same needle at the time of injecting isoniazid, the solutions being made up in separate syringes. Doses range from 25 to 75 mg. of streptomycin according to weight.

Isoniazid. Isoniazid (5-7 mg. per lb. of body weight daily in four doses) is given as ‘rimifon’ and oral administration is continued throughout treatment in conjunction with streptomycin or P.A.S. It is injected intrathecally, 25-50 mg. according to weight, daily at the start of treatment (Table 1) until improvement as judged by clinical condition and C.S.F. changes becomes apparent. Thereafter injections are given on alternate days and the interval progressively lengthened provided that improvement continues. As confidence in the method was gained the duration was shortened. For injection the drug is dissolved in 2 ml. of sterile distilled pyrogen-free water.

P. Amino-salicylic Acid (P.A.S.). Para-amino-salicylic acid (7-18 g. daily in four divided doses according to weight) is given orally to all patients upon discontinuing streptomycin and continued in conjunction with oral isoniazid for several months. Dosage starting at a quarter
of the optimal is increased over a period of seven to 14

days according to tolerance to full dosage. By this means

intestinal disturbance is minimized and in no case have

vomiting and anorexia been sufficiently severe to warrant

more than temporary withdrawal or reduction of the dose.

The Patients

All patients suffering from tuberculous meningitis,
six adults and 12 children, admitted during the period
of the trial have been included (Table 2). Their ages
range from 11 to 53 years. Bacteriological confirmation
of the diagnosis has not been obtained in every case,
though in all there was no doubt on clinical grounds,
and the cerebrospinal fluids have been cytologically and
biochemically typical. Of the 18 patients, six were
classed as early, eight as intermediate and four as late.

At the time of diagnosis and the start of treatment,
three patients were in coma and six had impaired
consciousness of lesser degree. In eight neurological
lesions were already present. Two children are included
who had relapsed after previous treatment, one following
streptomycin therapy only and another after an inade-
quate course of streptomycin and oral isoniazid.

Isoniazid Levels in C.S.F.

In our earlier patients isoniazid concentrations in the
C.S.F. were not measured owing to the lack of a reliable
method. Estimations in four later cases were made by
the method described by Short (1954). Levels of 1·1,
0·05, 0·45 and 0·3 mg. per ml. were found in C.S.F.
24 hours after intrathecal injection while oral therapy
was maintained. In the second of these cases no isoniazid
could be detected on two subsequent occasions although
the concentration in the serum was 0·13 mg. per ml.
In the other cases the C.S.F. levels were of the same order
or rather less than those in the blood, so that they are

<table>
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<th>Case No.</th>
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<th>Intrathecal Dosage per lb. Body Weight (mg.)</th>
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<th>Death</th>
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<tr>
<th>Name</th>
<th>Case No.</th>
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<th>Consciousness</th>
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<td>Alert</td>
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probably due to diffusion from the blood and not to intrathecal therapy.

Therapeutic Results

In all patients the infective process has been controlled and only one has died while the cerebrospinal fluid has been still abnormal. One death occurred suddenly in a late case (Case 1) with severe dementia and quadriplegia six months after the end of treatment from secondary hydrocephalus. This child had received intrathecal isoniazid only from the third to the eighth week of the first course of treatment. The second course of treatment, which was instituted at the 18th week on account of relapse, consisted of intrathecal and intramuscular streptomycin and oral isoniazid. At the time of death the C.S.F. contained fewer than 10 lymphocytes, no polymorphs, protein 50 mg. % and sugar 55 mg. %. At necropsy no evidence of tuberculous disease, gross or histological, could be found in the meninges or brain and death is therefore attributed to hydrocephalus occurring as a complication of tuberculous meningitis which itself had healed.

The second death occurred in a marasmic adult aged 33 who was transferred from a mental hospital where he had been a patient on account of schizophrenia. On admission he was in deep coma, with hemiplegia and multiple pressure sores. In spite of combined therapy and cortisone there was no clinical improvement and he died on the 49th day. At that time the cerebrospinal fluid contained sugar, 50 mg. per ml., protein 210 mg. and 24 lymphocytes. At necropsy a small walled-off focus was present over the left hemisphere but no evidence of active meningitis. There was gross cerebral softening.

In Case 4, the situation is similar in that the infection has been controlled, but there is residual hydrocephalus, dementia and quadriplegia. This child had been treated previously with streptomycin only and at that time the neurological lesions had appeared. They were present when intrathecal isoniazid was begun at the time of her relapse, and, although this has been controlled, the cerebral damage has shown no improvement.

In no patient have complications appeared after the start of treatment and in all others recovery has been complete, apart from pre-existing neurological lesions. Pre-existing neurological lesions underwent some improvement during and after treatment as judged by clinical examination, and in only one besides that already mentioned has there been any significant disability. In no instance was there exacerbation that might be attributed to focal oedema (Ritchie, Taylor and Dick 1953).

A minor degree of optic atrophy with minimal constriction of the visual fields developed in Case 7 which had previously relapsed.

Side-effects

Central Stimulation. Two major epileptic seizures in close succession occurred in Case 8 (an adult) in the eighth week of treatment. This had suffered from convulsions in infancy, and the E.E.G. revealed a mild paroxysmal instability. Apart from some restlessness there were no other effects attributable to isoniazid, and since continued treatment did not provoke further convulsions, it is probable that isoniazid was at the most only a minor factor in its causation.

No other phenomena attributable to isoniazid toxicity on the central nervous system as described by Castle, Carr, Chamberlain, D’Esopo, O’Connor, Pfuetze, Tucker, Tempel and Ebert (1953) were encountered.

Meningeal Irritation. In two patients (Cases 3, 7) there were findings in the C.S.F. consistent with low-grade chemical meningitis. In both the C.S.F. protein steadily increased to 350 mg. and 800 mg. respectively, which diminished on withholding treatment.

The C.S.F. of the first patient also showed a pleocytosis (350 polymorphs per ml.) during treatment, which disappeared rapidly on withdrawal. The second patient at the time of the rise of C.S.F. protein developed a partial spinal block which resolved slowly but completely following withdrawal of intrathecal therapy. The long duration of the disease and its relapse could alone have caused the C.S.F. changes in this patient, and it is unlikely that isoniazid had any significant effect. In neither case did these reactions cause any permanent sequelae. While present there were mild symptoms of meningeal irritation, namely headache and occasional vomiting with poor appetite, which, though not severe enough in themselves to warrant stopping treatment, were unpleasant. In the first patient (Case 3), the youngest in the series, the dosage was by weight the highest (1.25 mg./lb.) and was perhaps more than was necessary. Our impression is that the severity of the meningeal reaction is comparable to that caused by streptomycin or penicillin when administered intrathecally.

Discussion

The reason for investigating the value of injecting isoniazid intrathecally when the present inclination is to reduce intrathecal treatment lies in the unfavourable results still encountered in advanced
disease and the desirability of bringing about further improvement.

Failures may be broadly divided into those cases which die before treatment can become effective, those in which permanent brain damage occurs and those which relapse through inability to eradicate the infection. While all are directly related to delay in instituting effective therapy, it is possible that even in such late cases a more rapid and complete antibacterial effect might prevent a proportion of these failures, and also permit some reduction in the duration of treatment.

The importance of rapid bacteriostasis in the prevention of early deaths is obvious. In preventing relapses it is likewise important, since the work of several investigators has clearly shown (Ritchie, Taylor and Dick, 1953; Dick, 1953 and 1954) that early lesions can undergo complete resolution and sterilization under the influence of chemotherapy whereas late foci merely become walled off and are not sterilized (Hobby, Lenert, Rivoire, Donikian and Pikula, 1953). In this connexion isoniazid possesses manifest advantages over streptomycin as less fibrosis occurs and more complete healing is allowed (Hobby et al., 1953), and is therefore an indispensable drug in any therapeutic régime.

It is thus necessary to determine whether there is room for greater efficiency in the use of available antibiotics. In practice this may be reduced to consideration first of the optimal therapeutic concentration and secondly of its attainment in the tuberculous focus. In the first place Lecoq and Linz (1952) have shown that a large number of microorganisms raise the minimal concentration of isoniazid necessary for inhibition, so that there may be need for higher minimal concentrations of isoniazid in late rather than in early disease. The question of whether concentrations of isoniazid which exceed the minimal offer any therapeutic advantage by possessing greater antibacterial activity has been studied by Fletcher (1953) and Barclay, Ebert and Koch-Weser (1953). They found little evidence to suggest that increasing the concentration increased inhibitory activity. Later, however, Singh and Mitchison (1954) found convincing evidence that the antibacterial effect is in fact enhanced. Furthermore the laboratory finding that isoniazid in high concentration reduces the viability not only of actively growing bacteria but also of resting organisms (Peizer, Widelock and Klein, 1954) must be considered as a potential therapeutic advantage.

As the tuberculocidal action of isoniazid is enhanced quantitatively and qualitatively by increasing its concentration, in practice a greater antibacterial effect would be expected and must be exploited by ensuring that the dosage and route of administration enable such concentrations to reach the microorganism.

The second point, namely the attainment of optimal levels at the site of infection, may under favourable conditions be satisfied by increasing the oral dosage. In tuberculous meningitis there are, however, special features which not infrequently interfere with free access.

Isoniazid diffuses from the blood stream to the C.S.F. with little fall in concentration (Fletcher, 1953), and inhibitory concentrations can be maintained in the C.S.F. after oral administration. In early cases there is probably no significant obstruction to the free flow of C.S.F. and the passage of the drug to the site of infection is unimpeded. On the other hand in late disease, exudate, which is insufficient to cause gross obstruction, may obstruct the capillary spaces of the sulci at whose bases lie the tuberculous foci and prevent free circulation of the drug. In these circumstances it may not be possible to bring adequate concentrations of drugs, such as streptomycin, which depend on free circulation of C.S.F., into contact with the organism.

With isoniazid, on the other hand, the only theoretical difficulty in obtaining optimal therapeutic local concentrations arises when the tuberculous focus is deeply buried in brain tissue and the blood supply is also impaired. In chronic lesions the zone of endarteritis and ischaemia which surrounds the focus may form a barrier to blood-borne agents. High concentrations may then only be obtainable by providing such high levels in the C.S.F. or blood that a small amount will permeate the ischaemic brain tissue to reach the site of infection. In normal brain the concentrations reached are probably lower than those in the blood, since Barclay, Ebert, Le Roy, Manthei and Roth (1953) have demonstrated that the concentrations in less vascular structures such as fat and bone are about one-half those in the blood. While they performed no estimations on brain tissue it is probable by analogy with the behaviour of other antibiotics than those of isoniazid are also low.

The state of a tuberculous focus itself appears to matter little; concentrations of isoniazid of the same order as those bathing the surface are rapidly obtained in its depths irrespective of the extent of fibrosis and exudate or the amount of caseous material (Barclay et al., 1953). Similarly isoniazid diffuses freely into the macrophage reaching a concentration similar to that outside the cell (Mackaness and Smith, 1952; Suter, 1952). In this respect it differs from streptomycin which virtually
fails to enter the cell and thus has little effect on intracellular microorganisms.

The therapeutic problem in advanced tuberculous meningitis is therefore seen to be caused as much by the changes in the surrounding tissues and blood vessels which hinder diffusion of antibiotic agents as by the character and size of the focus. In view of the potential advantages of concentrations of isoniazid which are higher than those generally accepted as sufficient and of the manifest difficulties in obtaining them at the tuberculous focus itself, as distinct from the body fluids, there is a strong argument in support of intensive therapy by combined local and systemic administration. Intrathecal administration of isoniazid with streptomycin in addition to high parenteral dosage provides means of ensuring optimal local concentrations. Toxic effects prohibit any increase in the parenteral dose of streptomycin and to a less extent of isoniazid, though with the latter a higher oral dosage, than is routinely employed e.g., 7-10 mg. per lb. body weight per day, has been used with apparent safety.

Intrathecal injection of isoniazid in the dosage employed has been shown in the present trial to be a safe procedure and reasonably free from side-effects due to non-specific irritation of the meninges. In our experience intrathecal dosage on the scale of 0.5 mg. per lb. of body weight is satisfactory both in respect of therapeutic efficiency and freedom from side-effects. While no detectable ill-effects occurred with a dosage of 1 mg. per lb., mild irritation was probably caused by a dosage of 1.25 mg. per lb. in one case and it is felt that 1 mg. per lb. may leave insufficient margin of safety. In the low-dosage range we gained the impression that the response to treatment was relatively slow with a dosage of 0.3 mg. per lb. or less.

Although estimations of the isoniazid concentration in the C.S.F. were made they do not indicate the highest levels obtained and for the reasons already given are of little value as a guide to the concentration in the tuberculous focus itself. The therapeutic response is considered to be the surest means of determining whether the local concentration is optimal.

Summary

The treatment of 18 patients suffering from tuberculous meningitis with intrathecal isoniazid is described.

In 17 cases the infection was eradicated. There were two deaths.

The side-effects of intrathecal isoniazid were few. In one infant on high dosage there was evidence of non-specific meningeal irritation which disappeared on withdrawal. In an adult with an abnormal electroencephalogram and a history of previous convulsions, two major epileptic attacks occurred, but treatment was continued.

The importance of rapid control of the infection and the therapeutic value of high local concentrations of isoniazid at the start of treatment are discussed.

I wish to thank Dr. S. R. M. Bushby of the Wellcome Physiological Research Laboratories for performing the isoniazid estimations, and Dr. J. S. Norell for his assistance in the early stages of the work.

References