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EDITORIAL

ANTIBIOTIC TREATMENT OF TYPHOID FEVER

The initial observations on the successful use of chloramphenicol in the treatment of typhoid fever[1] have been followed by many confirmatory reports. However, certain disadvantages, mainly relating to toxicity, have led to the investigation of other 'broad spectrum' antibiotics in this disease. These have proved disappointing on the whole. Aureomycin has been given extensive trial by some workers and the poor results generally described, as compared with those obtained with chloramphenicol, have been attributed to differences in the host-drug relationships in the two cases[2]. One worker[3] has reported that there is a symbiotic action when aureomycin is given in conjunction with chloramphenicol. Analysis of the results in his paper, however, do not altogether support this view and the findings appear no better than those usually produced with chloramphenicol alone. Terramycin has also been found to have only a moderate effect in the treatment of typhoid fever.[4]

Tetracycline, the newest of the 'broad spectrum' antibiotics, has been investigated and, from preliminary communications, results with this antibiotic also appear relatively unsatisfactory. In a series of 25 cases a poor response was obtained in 40%, a fair or incomplete response in 28%, and a good response in 32%.[5] These results are by no means impressive and are indeed little better than those obtained in the pre-antibiotic era when good nursing was the mainstay of treatment. In another series of patients treated with tetracycline, it was found that the average duration of pyrexia after commencement of therapy was almost twice as long as with chloramphenicol.[6] The comparative failure of the 'broad spectrum' antibiotics, other than chloramphenicol, in typhoid fever is not due to any difference in the susceptibility of the causative organism as measured by *in vitro* testing. Practically identical minimal inhibitory concentrations are found with all, including chloramphenicol.

Chloramphenicol remains the drug of choice in typhoid fever, and in doses of 500 mg. or 250 mg. every 6 hours, depending on the severity of infection, will produce defervesence in 3-4 days in the average patient.

Toxic effects of chloramphenicol appear to be largely related to the use of heavy loading doses. In a series

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DIE ANTIBIOTIESE BEHANDELING VAN MAAGKOORS

Die eerste waarnemings van die suksesvolle behandeling van maagkoors met chloramphenicol[1] is later deur 'n aantal verslae bevestig. Sekere nadele, hoofsaaklik in verband met toksisiteit, het egter as aansporing gedien om ander 'wye-spektrum'-antibiotika vir maagkoors te ondersoek maar die resultate was oor die algemeen teleurstellend. Sommige werkers het aureomycin baie deeglik uitgetoets en die resultate wat hul beskryf vergelyk swak met dié vir chloramphenicol; dit word aan die verskil in die 'gasheer-geneesmiddel'-verhouding van die twee gevalle toegeskryf.[2] Een navorser[3] het rapporteer dat 'n simbiotiese werking intree as aureomycin saam met chloramphenicol gegee word. Ontleding van die resultate wat hy aangee steun egter nie hierdie standpunt geheel en al nie en die resultate is oënskynlik nie beter as dié wat verkry word as chloramphenicol alleen gebruik word nie. Ook as terramycin gebruik word is gevind dat dit slegs 'n matige uitwerking op maagkoors het.[4]

Tetracycline, die jongste 'wye-spektrum'-, antibiotiese middel, is ook ondersoek en gegrond op voorlopige gegewens blyk die resultate onbevredigend. In 'n reeks van 25 gevalle was die reaksie in 40% swak, in 28% was dit middelmatig of nie volledig nie, en in 32% was dit goed.[5] Hierdie resultate is geensins indrukwekkend nie—inteendeel hul is maar weinig beter as wat behaal is in die tydperk vóór die antibiotika, toe goeie verpleging die hoeksteen van behandeling was. In 'n ander reeks pasiënte wat met tetracycline behandel is, is gevind dat nadat die behandeling begin is die koorsigheid gemiddeld ongeveer twee keer so lank[6] duur as wanneer chloramphenicol gebruik word. Hierdie betreklike mislukking van die 'wye spektrum' -antibiotika—met uitsondering van chloramphenicol—is nie aan enige verskil in die gevoeligheid van die veroorsakende organisme te wyte nie volgens *in vitro* toetse wat uitgevoer is. Feitlik identiese minimale stuitende konsentrasies word by almal, ook by chloramphenicol, gevind.

Chloramphenicol bly by voorkeur dié middel vir maagkoors. Dosisse van 500 mg. of 250 mg. elke 6 uur, na gelang die hewigheid van die aanval, sal gemiddeld binne 3-4 dae 'n afname in die siekte besorg.

Die vergiftigingsuitwerking van chloramphenicol staan oënskynlik grotendeels in verband met die toediening van swaar verhoogde dosisse. In 'n reeks van 330 gevalle waar in die begin 'n dosis van 3·5 g. gegee is, is vergiftigingsuitwerking in soveel as 44%[7] van die gevalle bespeur. Dit sluit in mislikheid, vomeer, huiduitslae en sekere geestesveranderings asook 'n vorm van vertraagde koors wat aan die geneesmiddel toegeskryf word. Die afskaffing van verhoogde dosisse het gelei

of 330 cases where an initial dose of 3·5 g. was given the incidence of toxic effects was as high as 44%.[7] These included nausea, vomiting, skin rashes, certain mental changes, and a form of delayed drug-fever. The abolition of loading doses resulted in a decrease of toxic effects without in any way diminishing the effectiveness of treatment.[8] In a series of 110 cases where no loading dose was given the incidence of toxic reactions was only 5%.[9]

Two forms of combined therapy have been recommended in recent years. The first of these is the administration of chloramphenicol along with TAB. The latter is given on the assumption that it will stimulate antibody formation, which might tend to be depressed by the antibiotic. This may well be a rational procedure in the first few days of illness, when it is known that antibiotics may depress antibody formation. In cases seen after the first week, however, the administration of chloramphenicol seems to have little effect on antibody production.

The second form of combined therapy is that of chloramphenicol along with cortisone. There is no doubt that occasionally in certain seriously-ill patients dramatic response is observed, with defervesence in 24-36 hours and great improvement in the general state. This form of therapy is not without its dangers and, theoretically at least, there is a risk that perforation may occur more readily in patients so treated. It is a form of therapy which should be restricted to those seriously-ill patients where the response to chloramphenicol alone appears to be less than usual.

Effective though chloramphenicol is in the great majority of cases of typhoid fever, its failure to influence the relapse rate or the incidence of complications is disappointing and the last word has not yet been said on the antibiotic treatment of this still common disease.

1. Woodward, T. E. *et al.* (1948): Ann. Intern. Med., **29,** 131.
2. Werner, C. A., MacDermott, W., Adams, C. and Du Bois, R. (1954): J. Clin. Invest., **33,** 753.
3. Ray, B. B. (1954): Indian Med. Gaz., **89,** 412.
4. Roy, H. K. and Das, A. (1952): Calcutta Med. J., **49,** 389.
5. Ruiz Sanchez, F., Ruiz Sanchez, A. and Granda, Q. F. E. N. (1955): Antib. and Med., **1,** 30.
6. Watson, K. C. (1955): Lancet, **1,** 646.
7. Marmion, D. E. (1952): Trans. Roy. Soc. Trop. Med. Hyg., **46,** 619.
8. El Ramli, A. H. (1953): Lancet, **1,** 927.
9. Watson, K. C. (1954): Trans. Roy. Soc. Trop. Med. Hyg., **48,** 526.

tot 'n afname in die vergiftigingsgevolge sonder om op enige manier inbreuk op die doeltreffendheid van die behandeling te maak nie.[8] In 'n reeks van 110 gevalle waar geen verhoogde dosis gegee is nie het slegs 5% van die gevalle tekens van vergiftiging getoon.[9]

In die laaste jare word twee vorms van gesamentlike behandeling aanbeveel. Die eerste is die toediening van chloramphenicol saam met TAB. Laasgenoemde word gegee omdat dit veronderstel word om die vorming van teenliggame aan te wakker, wat die antibiotiese middel geneig mag wees om te onderdruk. Dit mag wel in die eerste paar dae van die siekte 'n verstandige optrede wees gedurende welke tydperk dit bekend is dat die antibiotika die opbou van teenliggame mag onderdruk. In gevalle wat na die eerste week gesien is, blyk dit egter asof die toediening van chloramphenicol weinig uitwerking op die vervaardiging van teenliggame uitoefen.

Die tweede vorm van gesamentlike terapie is om chloramphenicol saam met cortisone te gee. By sekere ernstig siek pasiënte tree daar ongetwyfeld af en toe dramatiese verbetering in, die koors neem binne 24-36 uur af en 'n groot verbetering in die algemene toestand word bespeur. Aan hierdie behandeling is risiko's verbonde en teoreties altans bestaan daar die gevaar dat perforasie meer geredelik by pasiënte sal voorkom wat hierdie behandeling ondergaan. Hierdie vorm van terapie behoort tot dié ernstig siek pasiënte beperk te word wie se reaksies tot chloramphenicol alleen swakker is as wat gewoonlik die geval is.

Hoe doeltreffend ook al chloramphenicol in die groot meerderheid van maagkoorsgevalle mag wees, is dit teleurstellend dat dit nie slaag om die heraanvalsyfer te keer nie of om komplikasies te verhoed nie. Die antibiotiese behandeling van hierdie siekte wat nog so algemeen voorkom verg verder studie.

1. Woodward, T. E. *et al.* (1948): Ann. Intern. Med., **29,** 131.
2. Werner, C. A., MacDermott, W., Adams, C. en Du Bois, R. (1954): J. Clin. Invest., **33,** 753.
3. Ray, B. B. (1954): Indian Med. Gaz., **89,** 412.
4. Roy, H. K. en Das, A. (1952): Calcutta Med. J., **49,** 389.
5. Ruiz Sanchez, F., Ruiz Sanchez, A. en Granda, Q. F. E. N. (1955): Antib. en Med., **1,** 30.
6. Watson, K. C. (1955): Lancet, **1,** 646.
7. Marmion, D. E. (1952): Trans. Roy. Soc. Trop. Med. Hyg., **46,** 619.
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PETHIDINE ADDICTION

Pethidine is a synthetic analgesic introduced in 1939 and now widely used in therapeutics. It shares pharmacological properties of morphine and atropine. A large number of related compounds have been prepared but they have not come into general use. The exact site of the analgesic action is not definitely known but it is believed to be on cortical or sub-cortical structures. As with other sedative-analgesic drugs, patients may become psychologically dependent on pethidine.

The fact that it is an addiction-producing drug would not appear to need emphasis. Yet there is an increasing tendency to pethidine addiction sufficiently great to perturb the authorities.[1] Particular attention is drawn to the attitude of medical practitioners towards the drug, based on a widespread but mistaken belief that pethidine is less dangerous than morphine in producing addiction. Addiction is most likely to occur in psychopathic patients or in patients given large doses over a prolonged period, but there is a high incidence of primary pethidine addiction among doctors, nurses and members of associated professions.

Since pethidine was introduced a steadily increasing quantity of the drug has been consumed. In the United States 101,102 ounces were consumed in 1946, and

283,162 ounces in 1952. The number of pethidine addicts admitted to institutions in that country for treatment has correspondingly increased. Between 1 July 1950 and 30 September 1953 the addicts admitted to one large centre, the Public Health Service Hospital in Lexington, Kentucky, numbered 457, of whom 84% had sought treatment voluntarily. Of the 457 patients 76 were medical pratictioners, 79 were nurses, 2 were dentists, and 29 were from ancillary professions. In 1953 three-quarters of the addicts admitted to the hospital were males and one-quarter females. The majority of patients indicated that they had first received the drug from doctors. Some maintained their supply by forging prescriptions or stealing from hospitals where they were employed; some resorted to other drugs when their pethidine supply was restricted. Among the reasons given for the original taking of the drug were, for example, depression, anxiety, menstrual disturbance, alcoholic 'hangover', and pain.

It would be interesting to have statistics of pethidine addiction for other countries, including South Africa; probably the incidence here is higher than most doctors would expect. The drug is easily available and many are not fully aware of its dangerous character from the addiction point of view. The abstinence (withdrawal) symptoms are severe, but usually less so than with morphine. They develop within a few hours, with muscle twitchings and extreme restlessness as prominent signs. In South Africa the authorities are well aware of the dangers of pethidine; and the regulations under the Medical, Dental and Pharmacy Act require medical practitioners to take the same precautions in prescribing pethidine as the drugs whose habit-forming properties are better known in the profession.

The management of addiction is a specialized procedure. The combined medical, nursing and psychiatric treatment can best be carried out in special institutions, where a complete clinical and laboratory investigation is made before withdrawal therapy is undertaken. Rehabilitation measures will be necessary under the guidance of the psychiatrist.

1. Wld. Hlth. Org. Techn. Rep. Ser. 1955, No. 95.