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DIE TOEPASSING VAN UITGEREKTE STOLLING-BESTRYDENDE TERAPIE BY KROONSLAGAARSIEKTE

Stollingbestrydende middels word vandag dikwels gebruik in die behandeling van trombose-siektes. In die jare nadat hierdie soort behandeling vir die eerste maal toegepas is, is sy doenlikheid, sy veiligheid en sy terapeutiese doeltreffendheid druk bespreek. Sy toepassing in die beheer van die akute episode van kroonslagaartrombose word vandag deur feitlik alle klinieke goedgekeur. Daar is egter nog meningverskil oor die vraagstuk of sy gebruik beperk moet word tot ‚swak risiko'-gevalle (teenoor ‚goeie risiko'-gevalle) aangesien die voorkombare sterftesyfer by die ‚goeie risiko's' selfs minder as 0·8% kan wees.[1] Baie geneeshere verkies om dit by alle pasiënte te gebruik. Die terapeutiese proefnemings wat die doeltreffendheid van hierdie behandeling moes demonstreer kan nouliks as toonbeelde van wat sulke toetse behoort te wees, beskryf word; nietemin, en ten spyte daarvan dat sommige gesaghebbendes nog lank bly twyfel het, is die algemene mediese opinie vandag sterk ten gunste van hierdie behandeling. Dit is nie heeltemal duidelik juis waarom hierdie middels doeltreffend in die behandeling is nie. 'n Onlangse studie uit Oxford[2] beweer dat die algemene gebruik van stollingteenmiddels by hartspierinfarksie 'n skerp afname slegs in die sterftesyfer van long-propvorming teweeggebring het. Maar selfs al was dit die enigste gevolg, is dit twyfelagtig of 'n behoorlik uitgesoekte beheergroep (sonder sulke terapie) vandag bymekaar gemaak kan word om hierdie feit te staaf.

Dit begin nou lyk of hierdie middels vir lang periodes ná die aanval van miokardiese infarksie gebruik sal word. As dit moeilik was om hul waarde oor kort periodes te bepaal, sal dit des te moeiliker gaan om dit oor 'n lang tydperk te bereken. Die siekte is van so 'n aard dat die natuurlike geskiedenis lank en verskillend kan wees. Maar indien daar nie binnekort 'n ernstige poging aangewend word om hul doeltreffendheid te bepaal nie, kan dit onmoontlik word as die behandeling eers as ‚roetine' aanvaar word.

Snaaks genoeg was dit die neuroloë wat die eerste weggespring het. Reeds in Mei 1942[3, 4] het hulle begin met 'n toets van onafgebroke behandeling met dicoumarol by gevalle van verspreide sklerose. Nichol en Fassett[5] was seker die eerstes op die gebied van die kardiologie. Hulle het 5 pasiënte behandel met dicoumarol oor periodes van 6 tot 32 maande. Nichol is ook een van die medewerkers aan een van die jongste verhandelinge oor hierdie onderwerp.[6] 'n Aantal verslae van pasiënte wat oor selfs langer tydperke behandel is, is ook reeds voorgelê. Die meeste van hierdie toetsreekse was ‚sonder beheergroepe' uitgevoer, en vergelyk die sterftesyfers van die behandelde serie met verslae van pasiënte wat behandel was in die jare voordat stollingbestrydende terapie toegepas is of met die een of ander reeks

EDITORIAL

THE USE OF PROLONGED ANTICOAGULANT THERAPY IN CORONARY ARTERY DISEASE

Anticoagulant drugs are now widely used in the treatment of thrombotic states. In the years following the introduction of this type of treatment there was a great deal of discussion about its feasibility, safety and therapeutic effectiveness. Practically all clinics have now endorsed its use in the management of the acute episode of coronary thrombosis. There is still some divergence of view on the question whether its use should be restricted to 'poor risk' cases (as contrasted with 'good risk' cases) since the preventable mortality in the 'good risk' cases may not exceed 0·8%.[1] Many physicians prefer to use it in all cases. The therapeutic trials which demonstrated the effectiveness of this treatment could hardly be described as models of what a well conducted therapeutic trial should be; nevertheless, despite a lingering doubt in some quarters, the consensus of medical opinion is strongly in favour of its use. Why these drugs are useful in treatment is not particularly clear. A recent study from Oxford[2] maintains that the widespread use of anticoagulants in myocardial infarction has resulted only in a striking reduction of the number of deaths from pulmonary embolism. But even if this was the only effect it is doubtful if an adequately selected control group (without such therapy) could be obtained today to prove it.

It is beginning to look as if these drugs will be used for prolonged periods after the attack of myocardial infarction. If their value is difficult to assess over a short period it is even more so over a long period. The disease is one in which the natural history may be long and varied. Yet, if a serious attempt to assess their efficacy is not made soon, it may become impossible once the treatment becomes accepted as a 'routine'.

Curiously enough, the neurologists were first 'off the mark'. They started a trial of continuous treatment with dicoumarol in cases of disseminated sclerosis as early as May 1942.[3, 4] Nichol and Fassett[5] were probably the first in the field of cardiology. They treated 5 patients with dicoumarol for periods ranging from 6 to 32 months. Nichol is also associated with one of the most recent papers on this topic.[6] There have now been a number of reports of patients treated for longer periods. Most of these series were 'uncontrolled,' and compared the mortality of the treated series

pasiënte wat in baie opsigte van die ‚behandelde' groep verskil het. Aangesien dit goed bekend is dat ernstige foute gemaak kan word wanneer sulke breed verskillende groepe met mekaar vergelyk word, het die meeste geneeshere verkies om nie dadelik 'n oordeel uit te spreek oor die doeltreffendheid van hierdie behandeling nie.

In die afgelope paar jaar het 'n paar verhandelinge verskyn waarin die pogings om 'n behoorlik beheerde serie op te stel ietwat meer suksesvol is. Een van die eerstes is in 1953 in hierdie *Tydskrif*[7] gepubliseer en is later aangevul en uitgebrei. Suzman *et al.* het bevind dat daar 'n veelseggende verskil was tussen die stollingteenmiddelgroep en die beheergroep wat sterftesyfer en gevaar op herhaling betref. Hulle het tot die slotsom gekom dat wanneer die infarksie nie alleen die eerste aanval is nie maar ook van ligte aard is, en wanneer stollingteenmiddels gedurende die akute stadium toegedien word, die daaropvolgende prognose gunstig blyk te wees afgesien daarvan of die stollingbestrydende terapie vir 'n onbepaalde tyd voortgesit word of nie. As die presenterende aanval van infarksie egter ernstig of herhalend is, word die uiteindelike prognose gewoonlik heelwat rooskleuriger gemaak deur onafgebroke langtermyn terapie van stollingbestryding, maar daarsonder is daar baie min hoop op verbetering. In die afgelope paar maande het twee verdere verhandelinge verskyn. In 'n artikel wat hy vrymoedig ‚Die voorkoming van miokardiese infarksie' noem, doen Manchester[9] verslag oor die studie van 712 pasiënte wat vóór die proefneming een of meer infarksies gehad het; alternatiewe pasiënte is met stollingteenmiddels behandel. Hy beweer dat die behandeling in alle ander opsigte dieselfde was vir al die pasiënte. Daar was 3 maal soveel infarksies onder die pasiënte in die beheergroep as in die behandelde groep, en die sterftesyfer in eersgenoemde groep was 8 maal groter as in laasgenoemde. Manchester sê dat die behandeling by die indiwidu aangepas moet word, maar hy sluit die ontwikkeling van 'n trombo-emboliese komplikasie en ook 'n familiegeskiedenis van infarksie by 'n jong mens in by sy positiewe aanduidings vir behandeling.

Dit was oorgelaat aan Noorweë om die beste studie van hierdie probleem wat tot dusver gepubliseer is te lewer, asook die beste oorsig van voorheen gepubliseerde werk. In 'n beheerde kliniese studie[10] is 277 pasiënte een na die ander behandel vir akute miokardiese infarksie tussen Julie 1950 en Julie 1953, en is hulle opgevolg tot aan die einde van 1956. Al die pasiënte is met stollingteenmiddels behandel gedurende die akute stadium, en die seleksie van gevalle is eers ná die eerste maand van die behandeling gedoen. Pasiënte opgeneem in sekere afdelings van die hospitaal het onafgebroke behandeling met stollingbestrydende middels ontvang, terwyl die behandeling daarmee van pasiënte in ander afdelings van die hospitaal gestaak is ná 'n maksimumtydperk van 'n maand. Aangesien die verwysing van pasiënte na verskillende dele van die hospitaal deur 'n buitemuurse agentskap waargeneem was en nie onder die beheer van die navorser gestaan het nie, was die seleksie grotendeels onbevooroordeeld. Te oordeel na 'n gedetailleerde statistiese ondersoek van die vergelykbaarheid van die behandelde en die beheergroepe, kan dit aangeneem word dat die pasiënte heel per toeval in hulle besondere groepe verdeel is. Al die pasiënte is noukeurig nagegaan en 'n poging is aangewend om toe te sien dat die kardiologiese behandeling wat die beheergroepe ontvang het net so deeglik was as dié van die behandelde groep, afgesien van die stollingteenmiddels. Die finale resultate is statisties

with records of patients treated in years before the introduction of anticoagulant therapy or with some other series of patients differing in many material respects from the 'treated' group. Since it is widely recognized that grave errors are liable to arise when two such unequal groups are compared, most physicians preferred to suspend judgment on the efficacy of this treatment.

In the last few years a few papers have been published where the efforts at producing an adequate controlled series have been a little more successful. One of the earliest of these was published in this *Journal* in 1953,[7] the work being later amplified and extended.[8] Suzman *et al.* found a highly significant difference between the anticoagulant group and the control group in respect of mortality and risk of recurrence. They concluded that when the infarction is not only the first attack, but is also mild, and anticoagulants are given during the acute phase, the subsequent prognosis appears to be favourable irrespective of whether the anticoagulant therapy is continued indefinitely or not. By contrast, when the presenting attack of infarction is severe or is recurrent, the ultimate prognosis is likely to be significantly improved by continuous long-term anticoagulant therapy, without which the outlook is extremely poor. In the last few months 2 further papers have appeared. Manchester,[9] in a paper boldly entitled 'The prevention of myocardial infarction,' has reported a study of 712 patients who had one or more infarcts prior to the study, alternate patients being placed on anticoagulant drugs. It is claimed that treatment was, in all other respects, identical. There were 3 times as many infarcts in the control group as compared with the treated group and the mortality in the former was 8 times that of the latter. Manchester says the treatment must be individualized, but includes in his positive indications for treatment the development of a thrombo-embolic complication and also a family history of infarction in a young person.

It remained for Norway to produce the best study of this problem published to date, as well as the best review of previously published work. In a controlled clinical study[10] 277 consecutive patients treated for acute myocardial infarction during the period July 1950 to July 1953, were followed up until the end of 1956. All patients received anticoagulants during the acute episode, and the selection of cases was made only after the first month of treatment. Patients admitted to certain sections of the hospital received continuous treatment with anticoagulants, while with patients in other sections of the hospital anticoagulants were discontinued after a maximum period of 1 month. Since allocation of patients to different sections of the hospital depended on an outside agency and was not under the control of the investigator, the selection was to a large extent unbiased. A detailed statistical examination of the comparability of the treated and control groups provided a good basis for concluding that the patients were allotted by chance to

ontleed en die skrywer het opgesom dat daar by pasiënte *onder* 60 jaar in die groep wat dié behandeling ontvang het 'n veelseggende daling was in die voorkomssyfer van herhalende infarksie asook in die sterftesyfer gedurende die eerste 12 maande ná 'n akute verstopping. Die voorkomssyfer van herhalende infarksie en die sterftesyfer gedurende die eerste 12 maande by pasiënte *oor* die 60 was laer in die behandelde as in die beheergroep, maar nie soveel laer dat dit statisties van belang was nie. Klaarblyklik het pasiënte met nuwe primêre infarksies nie beter gevaar op die stollingteenmiddels as dié wat nie hierdie middels gebruik het nie—'n feit skerp in teenstelling met die bevindings van Suzman *et al.*[8] en Wright *et al.*[11] Die tydperk van 12 maande was arbitrêr gekies en die syfers skyn daarop te dui dat die verskil die grootste was binne die eerste 6 maande. Hoewel daar geen verskil te vinde was tussen die behandelde en beheergroepe ná die eerste 12 maande nie, is die moontlikheid dat die behandeling tog 'n uitwerking kan hê, nie geheel en al uitgesluit nie.

Die resultate skyn eners te wees met 'n verskeidenheid van stollingbestrydende middels. Daar is 'n paar skrywers wat uitgerekte behandeling met heparin aanbeveel, maar pasiënte wat dit probeer het, is dikwels ongeneë om daarmee aan te hou. Dicoumarol is die middel wat in die algemeen die meeste gebruik is, maar sy plek word al meer en meer ingeneem deur middels soos fenindioon. Blykbaar verskil die resultate maar weinig, en die keuse is grotendeels 'n saak van eie ondervinding en plaaslike gewildheid. Nuwe stollingbestrydende middels is vandag beskikbaar, maar hulle besit nie juis enige voordele wat die ouer middels nie het nie. Hulle uitwerkings is baie eners. Hulle vereis almal berekening van die protrombienbekwaamheid.[12] Die meeste pasiënte is verbasend stabiel wat hul behoeftes betref en dit is glad nie 'n ongewone ding dat die dosis jare lank dieselfde bly nie. By hierdie soort pasiënt is dit dikwels onnodig om meer dikwels as 6-8 maal per jaar toetse uit te voer. Die geoefendes ondervind min moeilikheid met die behandeling—dikwels is die grootste moeilikheid eintlik dat die pasiënt agtelosig word en nie kan onthou of hy sy pil gesluk het of nie!

Hoe lank behoort die behandeling te duur? As 'n bietjie voorkoming goed is, sou baie voorkoming nie beter wees nie? Moet alle mansmense op 13-jarige leeftyd begin met die terapie, of moet 'n mens wag op die eerste tekens van die siekte? Moet ons wag vir die eerste infarksie of kan ons uitstel tot na die tweede? En as die infarksie eers voorgekom het, moet die pasiënt vir die res van sy lewe behandel word of slegs vir 'n jaar. Dit blyk dat die behandeling wel nuttig is—maar die juiste indikasies daarvoor moet duideliker omskryf word. Dit is te hope dat beter beheerde proefnemings eendag hierdie probleme sal oplos—miskien nog voordat die metaboliese en endokrinologiese aanval in hierdie siekte daarin slaag om dit heeltemal af te skaf.

1. Russek, H. I. en Zohman, B. L. (1957): J. Amer. Med. Assoc., **163**, 922.
2. Honey, G. E. en Truelove, S. C. (1957): Lancet, **1**, 1155 en 1209.
3. Putman, T. J. (1943): Bull N.Y. Acad. Med., **19**, 301.
4. Putman, T. J., Chiavacci, L. V., Hoff, H. en Weitzen, H. G. (1947): Arch. Neurol. Psychiat., **57**, 1.
5. Nichol, E. S. en Fassett, D. W. (1947): Sth. Med. J. (Bgham., Ala.), **40**, 631.
6. Nichol, E. S., Keyes, J. N., Borg, J. F., Coogan, T. J., Boehrer, J. J., Mullins, W. L., Scott, T., Page, R., Griffith, G. C. en Massie, E. (1958): Amer. Heart J., **55**, 142.
7. Goldberg, B. en Suzman, M. M. (1953): S. Afr. T. Geneesk., **27**, 389.
8. Suzman, M. M., Ruskin, H. D. en Goldberg, B. (1955): Circulation, **12**, 338.
9. Manchester, B. (1957): Arch. Intern. Med., **100**, 959.
10. Bjerkelund, C. J. (1957): Acta med. scand., **158**, bylae 330.
11. Wright, I. S., Bourgain, R. H., Foley, W. T., McDevitt, E., Gross, C., Burke, G., Simon, E., Lieberman, J., Symons, C. en Heubner, R. (1954): Circulation, **9**, 748.
12. Toohey, M. (1958): Brit. Med. J., **1**, 252.

either group. All patients were carefully followed and an effort was made to give the control groups as thorough cardiological supervision, apart from anticoagulants, as the patients in the treated group. The final results were analysed statistically and the author concluded that in the group on anticoagulants there was, in patients under the age of 60 years, a significant reduction both in the incidence of recurrent infarction and in the mortality during the first 12 months after an acute infarct. The incidence of recurrent infarction and mortality in patients over the age of 60 years was lower in the treated than in the control group in the first 12 months but did not reach statistical significance. Patients with new primary infarction did not seem to do better with anticoagulants than those who did not receive these drugs, which is in marked contrast to the conclusions of Suzman *et al.*[8] and also to those of Wright *et al.*[11] The figure of 12 months was chosen arbitrarily and the figures seemed to indicate that the difference was greatest in the first 6 months. While no difference was found in the treated and control groups after the first 12 months the possibility that treatment might have an effect was not entirely excluded.

The results appear similar with a variety of anticoagulant drugs. A few authors advocate prolonged treatment with heparin, but patients who have tried it are often reluctant to continue its use. In the main, dicoumarol has been the drug most used , but it is largely being superseded by drugs such as phenindione. The results do not appear to differ a great deal and it is largely a matter of experience and local preference. New anticoagulant drugs are now available but have few obvious advantages over the older ones. Their actions are largely similar. They all require estimation of prothrombin efficiency.[12] Most patients are surprisingly stable in their requirements and it is not at all unusual for the dose to remain unchanged for years. Tests in this sort of patient may not need to be done more often than 6-8 times a year. In experienced hands the treatment gives little difficulty—in fact the chief trouble often is that the patient gets careless and cannot remember whether or not he has taken his pill!

How long should the treatment continue? If a little prevention is good is a lot not better? Should all males start therapy in their 13th year or should one wait for the first evidence of the disease? Should we wait for the first infarct or the second? After the infarct should treatment be for the rest of the patient's life or only for a year? It appears that the treatment does some good—but the exact indications remain to be more closely defined. It is to be hoped that more adequately controlled trials will one day give an answer to these problems—perhaps even before the metabolic and endocrinological attack in this disease succeeds in abolishing it altogether.

1. Russek, H. I. and Zohman, B. L. (1957): J. Amer. Med. Assoc., **163**, 922.
2. Honey, G. E. and Truelove, S. C. (1957): Lancet, **1**, 1155 and 1209.
3. Putman, T. J. (1943): Bull. N.Y. Acad. Med., **19**, 301.
4. Putman, T. J., Chiavacci, L. V., Hoff, H. and Weitzen, H. G. (1947): Arch. Neurol. Psychiat., **57**, 1.
5. Nichol, E. S. and Fassett, D. W. (1947): Sth. Med. J. (Bgham., Ala.), **40**, 631.
6. Nichol, E. S., Keyes, J. N., Borg, J. F., Coogan, T. J., Boehrer, J. J., Mullins, W. L., Scott, T., Page, R., Griffith, G. C. and Massie, E. (1958): Amer. Heart J., **55**, 142.
7. Goldberg, B. and Suzman, M. M. (1953): S. Afr. Med. J., **27**, 389.
8. Suzman, M. M., Ruskin, H. D. and Goldberg, B. (1955): Circulation, **12**, 338.
9. Manchester, B. (1957): Arch. Intern. Med., **100**, 959.
10. Bjerkelund, C. J. (1957): Acta med. scand., **158**, suppl. 330.
11. Wright, I. S., Bourgain, R. H., Foley, W. T., McDevitt, E., Gross, C., Burke, G., Simon, E., Lieberman, J., Symons, C. and Heubner, R. (1954): Circulation, **9**, 748.
12. Toohey, M. (1958): Brit. Med. J., **1**, 252.