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EDITORIAL

ORAL PREPARATIONS FOR DIABETES MELLITUS

Insulin is really a remarkably good drug for the treatment of the carbohydrate abnormalities of diabetes. Unfortunately, although it has very largely abolished acute diabetic deaths in coma, it has not prevented—in fact it has unmasked—the 'vascular degenerative complications'. The second drawback is that it is inactive by mouth, nor does it appear likely that any preparation of this polypeptide hormone will be made for oral administration. Many other substances have been mooted and have been tried as oral anti-hyperglycaemic agents. Decamethylene diguanidine ('Synthatin A') apparently was able to reduce blood sugar, but was too damaging to the liver. Cobalt compounds, which cause destruction of alpha cells of the islets of Langerhans, are likewise too toxic. Diethyl dithiocarbamate, which has been effective in certain experimental types of diabetes, is too unreliable. Oestrogens will apparently protect an animal against the destruction of the beta cells of the pancreas caused by alloxan, but have no action in human diabetes. There is a theoretical basis for the trial of nicotinic acid but, if this has any effect at all, it is certainly not great. In the Eastern districts of the Cape a herb known as *bitterblaar*, and sold there as 'vinca' and 'covinca' is taken by diabetics, but there is no good evidence of its efficacy. Recently there have been a number of unethical products offered for sale, consisting of mixtures of up to a dozen substances or extracts of doubtful potency. The great danger of these preparations is obvious. The severe insulin-requiring diabetic omits his injections and arrives at hospital in coma.

Now we have a new substance, elaborated in Germany, known as BZ55 or 'carbutamide'.[1,2,3] It was observed that certain sulphonamides were able to reduce the blood sugar and even produce symptoms of hypoglycaemia in normal animals, but these early compounds caused damage to the liver. The newer sulphonamide derivative N-sulphanilyl-N^1-n-butylurea, or carbutamide, however, was found to retain the blood-sugar-lowering properties but to be devoid of acute toxic properties.

VAN DIE REDAKSIE

MONDELIKSE PREPARATE VIR DIABETES MELLITUS

Insulien is 'n besonder goeie middel vir die behandeling van die koolhidraat-stoornisse van suikersiekte. Hoewel dit die akute diabetiese koma-sterftes grotendeels opgehef het, het dit ongelukkig nie die ‚ontaardingskomplikasies van die bloedvate' vermy nie; insulien het inteendeel hierdie komplikasies ontmasker. Die tweede nadeel is dat dit mondeliks onwerksaam is, en dit is blykbaar onwaarskynlik dat enige preparaat van hierdie polipeptiede-hormoon vervaardig sal word vir mondelikse toediening. Baie ander stowwe is reeds oorweeg en probeer as mondelikse middels teen hiperglisemie. Dekametileen diguanidien (‚Synthatin A') was blykbaar in staat om die bloedsuikergehalte te verlaag, maar het té beskadigend op die lewer ingewerk. Die kobaltverbindings wat die alfa-selle van die eilandjies van Langerhans vernietig, is ook te vergiftigend. Diëtiel-ditiokarbamaat was effektief by sekere eksperimentele soorte suikersiekte, maar is te onbetroubaar. Die estrogene beskerm 'n dier blykbaar teen die vernietiging deur alloksaan van die beta-selle van die alvleesklier, maar dit het geen uitwerking op menslike suikersiekte nie. Daar is 'n teoretiese grondslag vir die probeer van nikotinesuur maar, as dit wel nuttig is, is sy invloed maar baie gering. In die oostelike distrikte van die Kaapprovinsie word 'n kruid wat bekend is as ‚bitterblaar' wat bemark word as ‚vinca' en ‚covinca', deur suikersiektelyers gebruik, maar daar is geen afdoende bewys dat dit doeltreffend is nie. In die afgelope tyd is 'n aantal onetiese middels bemark, bestaande uit omtrent 'n dosyn stowwe en ekstrakte van twyfelagtige krag. Dit is duidelik hoe gevaarlik hierdie preparate is. Die akute insulien-behoewende lyer laat sy inspuitings vaar, met die gevolg dat hy in 'n koma by die hospitaal aankom.

Nou het ons 'n nuwe middel, vervaardig in Duitsland, wat bekend staan as BZ55 of ‚karbutamied'.[1,2,3] Dit was opgemerk dat sekere sulfonamiede in staat is om die bloedsuikergehalte te verlaag en selfs om simptome van bloedsuikergebrek in normale diere te veroorsaak, maar hierdie vroeë verbindings was beskadigend vir die lewer. Dit blyk egter dat die jonger sulfonamiedderivaat, N-sulfaniliel-N^1-n-butielurea, of karbutamied, wel in staat is om die bloedsuiker te verminder terwyl

No extravagant claims are made for carbutamide. Two years of trials in Germany have led to certain tentative conclusions. First, in the doses recommended, the compound is apparently almost non-toxic; one case of jaundice has occurred during its employment, not necessarily because of it; some reduction of white-cell count has been observed, but not agranulocytosis; drug rashes and drug fever have been reported; severe hypoglycaemia has not been seen unless the patient was also taking insulin at the same time.

Secondly, it seems as if carbutamide will prove of little or no value in the severe or brittle diabetes of the 'growth' type. This is a pity, because we really do need something which might act as an adjuvant to insulin in such cases, allowing easier and safer stabilization on a lesser dose. This problem has still to be investigated further—for instance, no reports have yet been seen on the use of carbutamide in the very severe diabetes of chronic pancreatitis.

Carbutamide is evidently able very significantly to reduce the blood sugar in the milder 'maturity' type of diabetic, especially if the condition is of short duration. It may well be able to control such patients who are on low carbohydrate diets and taking small doses of insulin. Unfortunately these are just the patients who need oral treatment the least—they are usually obese and a weight-reducing diet is their primary necessity. Indeed it would be a great pity and a disservice if carbutamide were to be used as an easy short-cut to diabetic 'control' in such patients, who were then to be allowed to take a free diet and to remain fat.

The exact mode of action of carbutamide is not known. At first it was thought to prevent formation of the blood-sugar-raising factor, glucagon, by damaging the alpha cells of the pancreas. It is more likely, however, that its action is peripheral—it seems to reduce the rate of destruction of insulin in the tissues. Consequently it increases the effectiveness of any insulin in the organism, whether endogenous or injected. This might explain why only those patients who have some circulating insulin of their own respond to carbutamide (i.e. the older 'mild type of diabetic'). The actual blood-sugar lowering is then due to the action of the 'protected' insulin, and not to the drug itself.

Because of our being as yet uncertain of the best use of carbutamide, many trials are still taking place in several countries, including South Africa. Until more is known from these trials it is strongly recommended that the drug should not be employed outside of hospitals in which careful control of the patient is possible.

1. Franke, H. and Fuchs, J. (1955): Dtsch. med. Wschr., **80**, 1449-1460.
2. Achelis, J. and Hardebeck, K., *Ibid.*
3. Bertram, 0. Bendfeldt, E. and Otto, H., *Ibid.*

dit terselfdertyd geen akute vergiftigende hoedanighede besit nie.

Daar word geen buitensporige aansprake vir karbutamied gemaak nie. Twee jaar van proefnemings in Duitsland het tot sekere tentatiewe gevolgtrekkings gelei. Eerstens is dié verbinding blykbaar so-te-sê onskadelik in die voorgeskrewe dosisse: een geval van geelsug het gedurende die gebruik daarvan voorgekom maar was nie noodwendig te wyte daaraan nie; daar was 'n sekere vermindering van die witseltelling, maar geen agranulositose nie; medisyne-uitslag en -koors is gerapporteer; tensy die pasiënt terselfdertyd ook insulien gebruik het, was daar geen akute bloedsuikergebrek nie.

Tweedens lyk dit of karbutamied van geen of baie min waarde sal wees by die hewige of ‚bros' suikersiekte van die ‚groei'-soort. Dit is jammer, want ons het waarlik iets nodig wat as 'n hulpmiddel vir insulien in sulke gevalle kan dien om op 'n klein dosis 'n makliker en veiliger ewewig te behou. Hierdie vraagstuk moet verder bestudeer word—daar is byvoorbeeld nog geen verslae oor die gebruik van karbutamied by die baie hewige suikersiekte van slepende alvleesklierontsteking nie.

Dit blyk dat karbutamied in staat is om die bloedsuiker baie aansienlik te verminder by die ligter ‚volwasse' soort suikersiekte, veral as die siekte nog nie lank bestaan het nie. Heel moontlik kan dit goeie beheer verskaf aan dié pasiënte wat koolhidraat-arm diëte hou en klein dosisse insulien gebruik. Ongelukkig is dit juis hierdie pasiënte wat mondelikse behandeling die minste nodig het—hulle is gewoonlik vet, en vir hulle is 'n verslankingsdieet die eerste vereiste. Dit sou jammer wees, en eintlik 'n ondiens, as karbutamied as 'n maklike kortpaadjie tot suikersiekte-‚beheer' by sulke gevalle gebruik word—die pasiëntc sou dan 'n vry dieet hou en vet bly.

Dit is nie presies bekend hoe karbutamied te werk gaan nie. Eers is dit gemeen dat dit die vorming van glukagon, die bloedsuiker-verhogende faktor, verhinder deur die alfa-selle van die alvleesklier te beskadig. Dit is egter meer waarskynlik dat sy werking periferaal is—dit vertraag blykbaar die vernietiging van insulien in die weefsels. Gevolglik vermeerder dit die werksaamheid van enige insulien in die organisme, hetsy endogeen of ingespuit. Moontlik is dit die rede waarom slegs dié pasiënte wat 'n sekere hoeveelheid van hul eie insulien in die bloedsomloop het reageer op karbutamied (d.w.s. die ouer, ‚ligte soort' suikersiekte). Die eintlike vermindering van die bloedsuiker is dus die gevolg van die ‚beskermde' insulien, en nie van die middel self nie.

Omdat ons nog nie seker is oor die doeltreffendste gebruik van karbutamied nie, word baie proefnemings nog steeds in verskillende lande en ook in Suid-Afrika gedoen. Totdat ons meer kennis ingewin het uit hierdie proefnemings, word dit sterk aanbeveel dat die middel nie buite hospitale—waar die pasiënt noukeurig beheer kan word—gebruik moet word nie.

1. Franke, H. en Fuchs, J. (1955): Dtsch. med. Wschr., **80**, 1449-1460.
2. Achelis, J. en Hardebeck, K., *Ibid.*
3. Bertram, F. Bendfeldt, E. en Otto, H., *Ibid.*