SOUTH AFRICAN MEDICAL JOURNAL SUID-AFRIKAANSE TYDSKRIF VIR GENEESKUNDE

Cape Town, 9 August 1969 Volume 43 No. 32 Deel 43 Kaapstad, 9 Augustus 1969

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YET ANOTHER SULPHONYLUREA FOR LATE-ONSET DIABETICS

We seem to have a surfeit of blood-sugar lowering agents for use in non-ketosis-prone, maturity-onset diabetics. The sulphonylureas available in this country include tolbutamide (Rastinon, Artosin), chlorpropamide (Diabinese), acetohexamide (Dimelor), tolazamide (Tolazine) and the closely-related glymidine or glycodiazine (Lycanol, Gondafon). In addition we have the diguanides, phenformin (Insoral) and metformin (Glucophage). Although there are minor differences between the sulphonylureas with regard to power and speed of action, mechanism of degradation, toxic effects and liability to cumulation and hypoglycaemia, by and large they affect the same people in the same way. If anything, the previously-believed differences among the sulphonylureas have recently been reduced. Thus it has become clear that all of them are usually equally effective whether given in a single daily dose or in divided doses, whatever their theoretical half-life times may be.[1]

It is also evident that severe and long-lasting hypoglycaemic coma can occur even from the so-called short-acting members of the family. Other severe side-effects have been gratifyingly rare with all these drugs, despite initial worries regarding jaundice and blood dyscrasias in relation to some of them. Consequently, one must seriously question what a new sulphonylurea has to offer and why one should be persuaded to use it in preference to old and trusted drugs of which one has had considerable experience.

The new drug now on the market is glybenclamide, tested under the cognomen HB419 and a joint product of the two German pharmaceutical houses, Hoechst and Boehringer-Mannheim (trade names Daonil and Euglucon). Since these two firms also produce and supply us with the popular and successful sulphonylurea, tolbutamide, they must have good reasons for launching a second one some 12 or 13 years later. The reason appears to be simply that glybenclamide is very many times more potent, weight for weight, in reducing blood-sugar levels than any other sulphonylurea so far marketed. This leads to the following possible advantages:

1. It may be more efficient in controlling diabetes.
2. The tablets are smaller and easier to swallow.
3. It may be cheaper.
4. It may have fewer toxic and side-effects.

Judging the relative efficacy of 2 sulphonylureas on an outpatient basis is extremely difficult in individual cases, unless the difference is very gross—one drug having no apparent action and the other producing excellent control. So many other variables enter into the test, such as natural fluctuation, unequal division of parties, emotional disturbances and personal bias, that one is, in effect, performing a very uncontrolled trial. To be sure of a partial superiority of one drug over another in an individual case would necessitate the alternate use of each drug several times. This we seldom do. It is therefore not surprising that opinion is divided concerning the relative efficacy of glybenclamide in comparison with other sulphonylureas.

In fact, as judged from the recent conference held on this drug in Bavaria,[2] and from the articles concerned with its trial in this country and reported in this issue of the *Journal*,[3-5] it would appear to be approximately as efficacious as chlorpropamide—slightly less so in some series. Of course the actual dose, weight for weight, is considerably less in the case of glybenclamide, the maximum recommended dose being 10 - 20 mg./day as against 500 mg. for chlorpropamide, but this makes little difference to the patient, except for the possibility of putting an equivalent dose in a smaller pill.

At the time of writing we are not aware of what the price will be or how it will compare with other sulphonylureas. Because of the large amount of chemical research work and pharmacological testing that culminated in glybenclamide, and also because of the rather complicated side-chain, it may be no cheaper than other sulphonylureas. At a normal dose rate of 1 or 2 tablets a day, the price per tablet will be able to be compared directly with that of chlorpropamide; but the price of 1 tablet of glybenclamide should be compared with that of 2 tablets of tolbutamide.

Toxicity has been shown by the makers to be very low—the toxic action seems not to have increased with therapeutic potency. Thus the oral LD_{50} of sodium glybenclamide in the albino mouse is 3·5 G/kg. and of tolbutamide 1·8 G/kg.,[6] while the LD_{50} of the original substance is over 15 G/kg. and of tolbutamide 2·5 G/kg.* Other studies give comparable results. As reported at the conference, there appear to have been no serious toxic effects among some 6,000 patients who had been concerned in trials of the drug, except possibly for 2 or 3 cases of jaundice which may have been coincidental. Minor side-effects were seen, as with all trials of new drugs, and even with placebos, but these were not severe and seldom led to discontinuation of the drug. There were a few allergic drug rashes, indicating that this sensitivity reaction may occur even with very small amounts of sulphonylureas. Schneider and Lopis[4] encountered several side-effects in their series, many of which, however, were probably not caused by the drug itself but possibly by the diguanide used in conjunction.

Although we may therefore expect toxic and side-effects to be minimal with glybenclamide, this is not the case with regard to hypoglycaemic reactions. These were not a feature in the reports in this issue of the *Journal*, but were frequently encountered by others as reported at the conference.[2] Some authorities suggested that glybenclamide should be used only after the less powerful tolbutamide had failed, particularly in old people or those

*Later figures from the manufacturers.

with very mild diabetes. It might be sufficient to remember that glybenclamide is highly potent in some individuals, and to be careful, therefore, to start with a very small dose in such circumstances.

As with other sulphonylureas, glybenclamide is not suitable for young diabetics who are liable to ketosis. It was reported from India that good control was frequently achieved in young diabetics (who were not ketosis-prone) and we shall probably find the same with South African Indians. Again, as with other sulphonylureas,[7,8] glybenclamide has been shown to combine well with the diguanides,[3,4] so that this combination may salvage many who would otherwise be failures on either drug alone. It is also clear that correct dieting will still be the cornerstone of diabetic management, as it is in treatment with insulin or any other drug. Again, as with other sulphonylureas, secondary failures do occur after initial months of satisfactory control, but the frequency of these is not yet certain. Many of them can be brought under control again if diguanides are used in conjunction.

Has this drug justified itself? We believe that it has. It is no panacea even for older diabetics, and there are several poor results in the presently reported trials.[3,4] It is in fact most unlikely that any further advance will be made in this class of oral drug. It may represent the ultimate sulphonylurea, and indeed it is to be hoped that we are not further deluged with similarly potent compounds produced by slight changes in the chemical side-chain but offering no increased advantage.

1. Vinik, A. I., Jackson, W. P. U., Marine, N. and Saxe, N. (1968): S. Afr. Med. J., **42**, 1257.
2. Tegernsee-Konferenz über das neue orale Antidiabetikum HB419, 27 - 29 January 1969.
3. Jackson, W. P. U. and Vinik, A. I. (1969): S. Afr. Med. J., **43**, 1002.
4. Schneider, T. and Lopis, S. (1969): *Ibid.*, **43**, 981.
5. Seftel, H. C. (1969): *Ibid.*, **43**, 979.
6. Farbwerke Hoechst AG (1967): HB419 Exposé.
7. Clarke, B. F. and Duncan, L. J. P. (1965): Lancet, **1**, 1248.
8. Jackson, W. P. U. (1967): S. Afr. Med. J., **41**, suppl. 1 July (S. Afr. G.P. Review).

FIKSHEID

Ons verbeter gedurig op ons sportprestasies. Daar is haas nie 'n sportbyeenkoms van enige omvang en status waar daar nie 'n paar bestaande rekords gebreek word nie. As mens in aanmerking neem dat noukeurige vasstelling en aantekening van sportprestasies nou reeds lank oral in die wêreld gedoen word, kom mens te staan voor die interessante vraag: Waar gaan dit eindig? As ons jaar na jaar vinniger atlete oplei en mense wat hoër kan spring of 'n diskus verder kan gooi dan moet daar tog seker op 'n gegewe stadium 'n eindpunt bereik word waar verby ons nie sal kan kom nie. Maar waar lê daardie absolute limiet?

Slegs 'n paar dekades gelede wou die beste afrigters nie graag byt aan die idee van 'n 4-minute myl nie. Dit sou darem eens te veel gevrae wees, het hulle geredeneer. Vandag is daar talle mense wat 'n myl in minder as 4 minute hardloop en sulke gebeurtenisse is nie eens meer koerantnuus nie. Wat nou van die 3-minute myl? Of is dit werklik te veel gevra om van ons atlete te verwag dat hulle ook hierdie grens moet oorskry?

Op feitlik alle gebiede van menslike prestasies behalwe die suiwer tegnologiese ontdekkings en atletiek, bestaan daar hoogtepunte wat erken word as feitlik onverbeterbaar. Die groot komponiste van die 19e eeu en vele skilders, digters en skrywers van vorige generasies sal altyd hul grootheid behou. Maar daar is skaars 'n atletiek rekord op enige van die sportgebiede wat nie gedurende die afgelope paar dekades 'n kerf hoër gestel is nie; soms selfs herhaaldelik. Daar is nie hoogspringers of spiesgooiers van 50 jaar gelede wie se rekords nou nog as asemrowende hoogtepunte in die sportgeskiedenis aanvaar word nie.

Hierdie feite in aanmerking nemende moet ons dus een van twee dinge aanvaar. Òf ons is vandag 'n veel beter en fisies sterker ras as ons voorvaders, òf dit is die beter kennis van die vereistes van afrigting wat die prestasies so indrukwekkend maak. In hierdie uitgawe publiseer ons 'n artikel oor die vereistes waaraan sportmanne van wêreldstandaard behoort te voldoen. Dit is interessant om te sien dat die skrywers tot die slotsom kom dat lang-afstand naellopers se prestasies nie noemenswaardig deur afrigting verbeter word nie. Dit is dus een afdeling waar ons die effek van verbeterde oefeningsmetodes kan negeer.

Dit is sekerlik waar dat die wêreld se gesondheidstatus oor die algemeen aan die verbeter is, maar sou dit so 'n groot verskil kan maak aan die sport rekords by Olimpiades? Geen land gaan tog sy chronies ondervoede burgers stuur om aan 'n internasionale byeenkoms deel te neem nie, en dus moet mens aanvaar dat die fiksheid van die hedendaagse atlete beter is as dié van hul voorvaders. Die mees waarskynlike verklaring vir ons gedurig verbeterende sportvermoë moet gesoek word in 'n samewerking tussen meerdere faktore: die verbetering in algemene gesondheidstatus; die beter afrigting; groter bewustheid van die belang van sulke prestasies en miskien nog vele ander dinge. As mens kyk na die foto's van sportspanne van weleer is dit opvallend hoe ondoeltreffend die kleredrag dikwels was en mens kry dan die indruk dat doelgerigtheid nie die eerste oorweging was nie.

Maar, soos reeds gesê, êrens sal dit moet ophou. Ons kan tog nie verwag dat met ons moderne gewilligheid om al die nodige te doen om prestasies te verbeter, die rekord nog tot in die verre toekoms jaar na jaar opgeskuif gaan word nie. Op die ou end sal ons die stadium moet bereik dat ons die uiterste van menslike inspanningsvermoë in die gesig staar, en dan sal die rekords jarelank onverbeterd op die boeke moet bly staan en die toekomstige atlete sal slegs kan probeer om die standaard te handhaaf, met min of geen hoop om ooit daarop te verbeter nie. Dit sal beslis neig om 'n dempende effek te hê op die geesdrif van die deelnemers en die toeskouers sal ook moet leer om nie gedurig asemrowende nuwe hoogtes te verwag nie.

Dit is 'n interessante raaispeletjie om te probeer voorspel presies waar die limiete gevind gaan word. Miskien moet ons nou 'n kassie êrens instel waarin die verskillende raaiskote geberg kan word, vir ons nasate om te ontdek en te sien hoe reg of verkeerd ons was.