Suid-Afrikaanse Mediese Tydskrif
South African Medical Journal

16 APRIL 1983 DEEL/VOLUME 63 NO. 16

Van die Redaksie/Editoral

Nuwe metodes van nitrogliserientoediening

Die vel word al sedert onheuglike tye as 'n medium vir die toediening van geneesmiddels gebruik, en ouer dokters sal hulle nog kan herinner aan die smeermiddels, mosterdpleisters, ens. wat deur ons voorvaders voorgeskryf is. Hierdie middels het waarskynlik nie veel meer gedoen as om net die vel rooi te maak nie en het in onguns geraak toe farmakologie in 'n meer presiese wetenskap ontwikkel het. Die lekedom het egter voortgegaan om hulleself in te smeer met middels wat na baie dekades nog 'n huishoudelike naam bly.

Maar die farmaseutiese industrie se navorsingsafdeling bevat deesdae 'n klomp vindingryke mense en die vel het onlangs weer gewild geraak, nie vir teenirritasie nie, maar vir die voorsiening van middels met sistemiese effekte. Dit ly min twyfel dat volgehoue toediening van 'n hele aantal middels via die vel uiteindelik sal bewys om 'n praktiese proposisie te wees, maar op die oomblik, behalwe hiossien, is die fokus op nitrogliserientoediening deur hierdie weg.

Sedert daar ontdek is dat nitrogliserien goed deur die vel geabsorbeer word, is studies om tegnieke te vind wat die egalige vloei van die aktiewe middel sal verseker, met toenemende entoesiasme voortgesit. Die gebruik van nitrogliserien in 'n salfbasis is goed bekend, maar die gebruik van salf is morserig en die dosering is nie maklik aanpasbaar nie.

Die probleem is natuurlik te wyte aan die feit dat die effek van sublinguale nitrogliserien op pasiënte met angina kortstondig is (die effekte neem drasties af na 2 minute), en dat die effek van die algemeen bekende isosorbieddinitraat langer is, maar nog steeds redelik kort is. Vir profilakse is pogings dus aangewend om 'n langwerkende of volgehoue vrystellingsvorm van nitraat te produseer om angina-aanvalle oor 'n tydsduur van etlike ure te verhoed. Menings hieromtrent verskil nog steeds aangesien die effekte grootliks individueel varieer volgens die pasiënt se vermoë om die middel op 'n eerste deurgang deur die lewer te metaboliseer. Volgehoue aksie (vir bv. ongeveer 8 uur) mag dus beteken dat dosisse isosorbieddinitraat toegedien moet word wat posturale hipotensie en akute hoofpyn mag veroorsaak.

Een manier om hierdie probleem te bowe te kom, is om die metaboliet isosorbied-5-nitraat te gebruik wat na bewering die eerste-deurgangeffekte in die lewer vryspring en daarom geheel en al biobeskikbaar is en verder betroubare bloedvlakke van die middel teweegbring. Hierdie produk is alreeds beskikbaar in Europa in 20 mg- en 40 mg-tablette, maar nog nie in Suid-Afrika nie. 'n Dosis van 20 mg of 40 mg 2-3 keer per dag word aanbeveel.

'n Ander manier is vanselfsprekend om die vel of mukusmembraan van die mond vir volgehoue vrystelling van nitrogliserien te gebruik. Die salf is alreeds genoem, maar binnekort sal 'n verdere ontwikkeling hier beskikbaar wees — die borskaspleister-tegniek. Drie trae vrystellingsaksiepreparate van kutane nitrogliserien is nou in die VSA te koop, elkeen gebaseer op 'n nitrogliserienreservoir wat aan die vel van die borskas of bo-arm kleef. Die pleister is bewys om sy nitrogliserieninhoud baie stadig af te gee, en word elke 24 uur omgeruil. Trouens, die aktiewe bestanddeel word ná 24 uur nog steeds afgegee, maar 24 uur is 'n gerieflike vervangtyd. Die werking van die pleister duur vir 30 minute nadat dit afgehaal is en die nuwe pleister neem 30 minute om 'n effektiewe bloedvlak te bewerkstellig, sodat 24 uur-beskerming wel moontlik is. Pleisters kom in meer as een grootte voor sodat die dosis van elke pasiënt tot 'n vlak getitreer kan word wat angina sonder newe-effekte (posturale hipotensie, hoofpyn) sal verhoed. Die enigste nadeel is die koste, maar pasiënte sal waarskynlik bereid wees om meer vir 'n een-maal-per-dag-toediening te betaal.

Vanselfsprekend kan die pleister met 'n beta-blokkeerder of met 'n mondelike kalsium-antagonis gekombineer word (indien laasgenoemde aangedui is).

In die VSA is daar nog 'n ontwikkeling, nl. die langwerkende transmukosale nitrogliserientablet. Hierdie tablet word onder die bolip geplaas en kleef effens aan die tandvleis vas. Dit los dan oor 'n tydsduur van 'n paar uur op terwyl dit 'n konstante uniforme dosis nitraat afgee. Aanvanklike proefnemings het getoon dat hierdie metode aanvaarbaar is vir pasiënte, en die dosis kan in 'n sekere mate getitreer word. Ons het teenswoordig nog geen nuus van hierdie tablet se vrystelling in Suid-Afrika ontvang nie.

Hierdie tegnieke is nuut en moet nog bewys om die toets van tyd te deurstaan, maar vroeë resultate was baie gunstig. Vir 'n gebalanseerde bespreking van die onderwerp en 'n verwysingslys word die leser na die November 1982-uitgawe van *Annals of Internal Medicine*, bl. 774, verwys, waarin daar 'n redaksionele artikel deur Reichek en Stutton verskyn met die gepaste titel 'Long-acting nitroglycerin for angina, 1982: Old dog, new tricks'.

Who compensates the injured research subject?

In recent years the ethical issues regarding clinical research have been widely discussed, and nowadays nearly all university centres appoint ethical committees to decide on the legitimacy of research proposals. Whereas a decade or two ago research activity was an almost private affair, current practice has lifted the veil of secrecy and subjected the researcher to peer review. Such accountability does indeed clip the wings of the enthusiasts, but it is generally welcomed as a safeguard for both the research subject and the investigator.

However, there is inconsistency in the present situation. Once a particular project has been approved and informed consent obtained, the formal administrative business is considered complete. Little if any specific attention is given by ethical committees to the question of compensation for accidents or injuries which may result from the research. Fortunately such events are rare, but they can impose real hardship.

In South Africa there is no legislation governing clinical research in human subjects. The common law dictates that liability is based on negligence, which means a lack of reasonable skill and/or a failure to take sufficient care, the burden of proof being on the injured party. The pharmaceutical industry may be negligent if its drug is inadequately tested, if the manufacture has been defective, or if information regarding the drug's safety is withheld. For example, a doctor is negligent if he prescribes a ß-blocker for a patient with a history of asthma; if negligence is proved, the defendant (the pharmaceutical industry or the doctor) will be required to compensate the patient. Medical practitioners usually belong to medical defence organizations which bear all the costs of an action for negligence, including the compensation awards.

Let us take the case of a patient who, in the course of a clinical trial with a new medicine, unexpectedly develops peripheral neuropathy. What recourse does he have to compensation? Peripheral neuropathy is an adverse effect which could not have been anticipated by either the experimental data or the present state of medical knowledge. No blame or fault can be attributed to any party and there is accordingly no basis for negligence in law. The hapless patient is thus left without a legal mechanism by which to seek recompense. This is clearly unsatisfactory, and the irony is that drug injury due to research is highly unlikely to be associated with negligence. Clinical research is the one setting where, because of a rigid protocol and strict monitoring, negligence is effectively excluded.

In the UK, the Royal Commission on Civil Liability and Compensation for Personal Injury in 1978 recommended *strict liability* as the basis of compensation for severe damage resulting from clinical research.[1] Strict liability denotes liability of the defendant irrespective of negligence and is based solely on proof that he caused the injury. In other words, to be entitled to compensation the patient must merely establish a causal connection between the medicine and peripheral neuropathy. It is of interest that the ethical committee of University College Hospital, London, will not generally consent to premarketing (and in some cases postmarketing) studies sponsored by pharmaceutical companies unless these companies accept responsibility for resultant injury even though they are not at fault.[2] Such a procedure provides adequate cover for patients who may come to grief, and it may be desirable that other research centres adopt it. However, much research work is not sponsored by industry, and indeed it may be entirely investigative and non-therapeutic.

Although strict liability appears to offer a just solution, it was not recommended by the Ciba Foundation Study Group.[1] Their objection was that the injured patient would be plunged into protracted litigation with its attendant stress, uncertainty and expense. Circumstances would force the patient and the researcher into adversary positions, a situation which would disturb the goodwill between medical researchers and the general public. Moreover, in order to protect themselves against claims, individuals or institutions would have to obtain appropriate insurance which, if available, would be very expensive (these patients are a high-risk group), and the costs thereof would probably have to be met from precious research monies.

The Ciba Foundation Study Group concluded that the most acceptable alternative was *no-fault compensation*, and they proposed that this scheme be administered by a non-judicial board. The compensation granted would be entirely independent of fault or blame, the only proof required being that injury resulted from the research. Awards would be made according to a prescribed scale of disabilities: minor or transient adverse effects would not be considered.

The scheme would be funded by a 'compensation pool' to which contributions would be made in varying proportions by the State, universities, pharmaceutical industries, the Medical Research Council and other interested bodies. The advantage of this system is that it involves no legal proceedings. The research subject and the investigator are thus not only spared the trauma of litigation but can work together in initiating and compiling a claim. Such collaboration will preserve, and even enhance, the spirit of mutual trust fundamental to clinical research. Obviously decisions about causation will sometimes be taxing, especially where the alleged injury can be interpreted as a complication of the pre-existing disease; in contentious cases, arbitration and appeal procedures may have to be set up. No-fault compensation schemes already operate in Sweden and New Zealand. The New Zealand Accident Compensation Corporation is a model on which other systems may be based. Richard Smith[3-5] has given a lucid and entertaining analysis of the merits and the problems of the New Zealand experience.

Those generous enough to submit to a clinical research programme are making a vital contribution to medical science, and it is essential that their participation be valued and that in the unlikely occurrence of misadventure they (and their dependants) be suitably compensated. In fact,

subjects should be assured before they enter a research study that no-fault compensation is available in the event of injury. If there is no entitlement to such compensation, then it may be proper to apprise them of this before they give informed consent.

Compensation for research accidents should not be the responsibility of a particular individual, hospital or pharmaceutical firm but should be borne by the community as a whole. It is society that will ultimately benefit from the research and it is only fair that society should compensate the victims of research. A national no-fault compensation scheme would seem to afford the most practicable arrangement to implement this goal. Ideally there ought to be a State insurance system for the entire population and for all types of disabilities, whether these are caused by accident or disease. Otherwise one invites the egalitarian charge that subjects in research are a favoured group who are rewarded for their injuries, whereas those who fall prey to disability in other circumstances have no 'scapegoat' and no hope of redress. But let the medical research fraternity put its own house in order first.

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