Lesson of the Week

Diminished activity of glyceryl trinitrate

M O'HANRAHAN, K McGARRY, J G KELLY, J HORGAN, K O'MALLEY

Glyceryl trinitrate is used under the tongue for the rapid relief of angina pectoris. Ideally, the tablets are rapidly absorbed and take effect in one to two minutes. It is well known that glyceryl trinitrate is unstable and that the tablets should be protected from light and extremes of heat and stored in glass bottles that do not contain cotton wool or other packing material.^{1 2} Although the tablets are supplied by the manufacturers in suitable containers, they are often stored under less than ideal conditions after leaving the manufacturer. We investigated whether loss of activity of glyceryl trinitrate occurred owing to poor storage by patients.

Methods

Twenty-one consecutive patients who attended a cardiac clinic and were taking glyceryl trinitrate for angina were interviewed and asked for a sample of their tablets. They were asked about the duration of storage of the tablets since dispensing, the normal place of storage, how often they took tablets, and whether the tablets were effective. In addition, the type of container, the presence and type of packing material, and the number of tablets remaining were recorded. After collection from patients the tablets were stored below 25° in individual dark glass bottles without any packing material. Eleven tablets were chosen using tables of random numbers and one each given to 11 healthy volunteers aged 20 to 29 years (mean 22.9 years). Each volunteer also received on different days a placebo tablet and a fresh tablet from a previously unopened manufacturer's container. The doses were given in random order and using a double-blind design. The heart rates and blood pressures of the volunteers were measured three times before the tablet was taken to establish a steady baseline. Measurements were also taken as the tablet was given and at intervals of 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, and 60 minutes thereafter. Volunteers remained seated during this period.

Changes in heart rate after each tablet were compared using a Student's *t*-test. Areas under the heart-rate time curve were calculated by the trapezoidal rule.

Results

Glyceryl trinitrate tablets were obtained from 20 patients. One patient did not normally carry her tablets. Sixteen had their

Glyceryl trinitrate tablets lose their effect if they are not stored properly

full supply with them, while four others had a further supply at home. Two patients carried glass bottles, 17 had plastic containers, and one kept the tablets wrapped in cloth. Eighteen containers provided protection from light but nine contained cotton wool and one had foam packing. From two to 100 tablets (mean 16) remained in the containers and the duration of storage was from three days to five years (mean 13 months). Some patients took tablets regularly—for example, several times a week—whereas others only occasionally used them.

The mean increase in heart rate produced at the various time intervals by each of the tablets is shown in the figure. The

Mean ($\pm$ SEM) increase in heart rate of 11 volunteers at 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, and 60 minutes after taking glyceryl trinitrate.

difference between the increase in heart rate caused by the fresh tablets and the increase caused by placebo was significant at all times up to 20 minutes ($p < 0.02$). Significant differences ($p < 0.05$ or less) between the patients' tablets and placebo occurred at most, but not all, times up to 15 minutes. The areas under the heart rate-time curves for fresh tablets and patients' tablets were estimated from the time of drug administration for 15, 20, and 30 minutes, and the difference between tablets was significant in each case ($p < 0.02$). Fresh tablets and those returned by patients could not be distinguished on the basis of symptoms reported by volunteers.

Discussion

The decreased activity of the patients' tablets compared with fresh tablets showed that storage by patients had an adverse effect on the quality of tablets. The increase in heart rate caused by the patients' tablets at 10 minutes was less than half that produced by the fresh tablets, and after 15 minutes the patients'

Department of Cardiology, St Laurence's Hospital, Dublin 7, and Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, St Stephen's Green, Dublin 5

M O'HANRAHAN, MPSI, research pharmacist

K McGARRY, MRCP, research fellow

J G KELLY, PhD, lecturer in pharmacology

J HORGAN, FRCP, consultant cardiologist

K O'MALLEY, FRCP, professor of clinical pharmacology

tablets did not produce an effect that was significantly different from placebo. The fresh tablets continued to cause an appreciable increase in heart rate until 20 minutes after administration, and an overall difference in effect (area under the curve) could be observed up to 30 minutes after administration.

Despite the inclusion of stabilisers in recent formulations of glyceryl trinitrate tablets,³⁻⁵ maintaining stability during use is still a problem. The importance of proper storage is well known medically, but clearly there is a failure in communication between doctor and patient since most patients normally stored their full supply of tablets for long periods under inappropriate conditions. Only two patients produced the recommended type of container, and one of these contained absorbent packing material. Though it is necessary for patients to carry a supply of tablets with them, they should be encouraged to carry only a small number of tablets in this way and to store the remaining tablets at home under the recommended conditions.

We therefore recommend that greater care should be taken in dispensing glyceryl trinitrate tablets to ensure that the containers

conform to the manufacturer's recommendations. The number of tablets prescribed at one time should be related to likely consumption, and care should be taken to ensure that patients understand the importance of proper storage.

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A 66-year-old woman was found to have primary hyperparathyroidism with a considerably raised serum calcium concentration. Two parathyroid adenomas were removed with excellent postoperative progress. She was prescribed calcium gluconate, eight tablets daily, postoperatively, though there was no tetany and the serum calcium concentration fell to only 1.8. Does calcium need to be continued? What risk is there of hypocalcaemia developing if calcium is stopped? If there is a risk, for how long does it last?

From the question, it seems likely that this woman had severe hyperparathyroid bone disease. Postoperatively, the serum calcium concentration almost invariably falls because of the "hungry bone" syndrome. This is due to rapid repair of the bone disease with a high influx of calcium into the skeleton. Vitamin D is almost always needed in severe cases in addition to calcium supplements. A convenient form of treatment would be to give 1 to 2 micrograms of 1,25 dihydroxy vitamin D (Rocaltriol) or 1 alpha hydroxy vitamin D (1 alpha) together with four to eight tablets of calcium supplements. Often high doses of calcium supplements give diarrhoea. The requirements for vitamin D and calcium supplements lasts for about a month, after which treatment can be slowly withdrawn over the course of a few weeks provided that normocalcaemia is maintained. If hypocalcaemia recurs as a long-term problem this suggests that the patient has postsurgical hypoparathyroidism, in which case the need for vitamin D supplements is likely to be permanent.—D J HOSKING, senior lecturer in medicine, Nottingham.

As most individuals carry herpes simplex virus (type 1), which they may excrete orally from time to time, and, as herpes simplex virus (usually type II) is associated with carcinoma of the cervix, is orogenital sex inadvisable on medical grounds?

The epidemiological relationship between herpes simplex virus, type 2, and carcinoma of the cervix is complex, and a true causal relationship has not been established. The aetiology of cervical carcinoma is probably multifactorial and includes such factors as age of first coitus and number of sexual partners, but much more work is needed before the picture becomes clear. Most investigations have shown that cervical dysplasia and carcinoma of the cervix occur more often in women with antibodies to herpes simplex virus, type 2, than in those without these antibodies. Further research work is needed, such as comparisons of women who have recurrent cervical herpetic infections with those who do not and the influence of the recurrence rate on dysplasia and carcinoma. The role of pre-existing type 1 antibody also needs investigation. Until the answers to some of these questions are available it is premature to state that the practice of orogenital sex is inadvisable on medical grounds because of the herpes simplex virus.—R D CATTERALL, consultant physician in genitourinary medicine, London.

Do pomades used for darkening grey hair contain any substance that might be a health hazard?

Yes. The active ingredient in proprietary remedies for restoring colour to grey hair is either a metallic salt, usually lead acetate, or a synthetic dye of the paraphenylene diamine series. Metallic salts work by forming a film on the surface of the hair that produces a gradual darkening of the hair as the layers build up; paraphenylene diamine dyes infiltrate the shaft of the hair itself and produce a rapid and permanent darkening. The lead is present in only small quantities and provided it stays on the hair is unlikely to be hazardous to health, but it is unwise to apply it to facial hair near the mouth or to hair on damaged or diseased skin as absorption is possible. Metallic dye products are popular at the moment and, sadly, many lead-containing products are not labelled with their constituents or with adequate warnings. In view of the current concern about the lead in our environment it seems unnecessary to permit this use of lead when other dyes are effective. Paraphenylene diamine dyes do induce contact hypersensitivity in a few otherwise normal individuals, but the risk is small. Other ingredients, such as the vehicle, may also contain potential allergens and even primary irritants, but their hazard is likewise small.—A B SHRANK, consultant dermatologist, Shrewsbury.

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A young woman had severe bronchitis after which she claims that everything smells bad. During the attack of bronchitis she temporarily lost her sense of smell. What might be the cause of her complaint and what treatment is advised?

This patient is suffering from a qualitative change in the sense of smell, or parosmia. It is necessary to exclude any local abnormality in the nose such as an infective rhinitis (secondary to a chronic sinus infection) or an allergic or vasomotor rhinitis. An infective rhinitis may give rise to a change in the sense of smell, and this is also seen in allergic or vasomotor rhinitis, but the sense of smell is usually less affected in these conditions. A viral infection, particularly of an influenzal nature, may damage the olfactory nerve fibres and when this occurs a greater or lesser degree of fibrosis of the neuronal tissue occurs with symptoms of parosmia. Psychogenic disorders, such as depression, may give rise to abnormalities in the sense of smell, and this possibility must be considered. The prognosis in the case of parosmia resulting from viral lesions is poor, and there is no specific treatment, but in time the symptoms may become less noticeable due to adaptation.—PHILIP BEALES, consultant ear, nose, and throat surgeon emeritus, Doncaster.

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