TRACE ELEMENT SUPPLEMENTATION WITH SOLUBLE GLASSES

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Many of the elements known to be essential for life are needed in very small quantities. For example, between 1 and 5 mg/day of copper, selenium, manganese, iodine and cobalt are sufficient for even rapidly growing or lactating farm animals (Underwood, 1977). Nevertheless deficiencies of these elements occur quite commonly and poor productivity and clinical disease may result. The deficiencies may be due either to a lack of the element in the diet or to interference by other elements with its availability, as, for example, on the teart pastures of Somerset, where high molybdenum concentrations in the herbage reduce the availability of copper to grazing cattle and sheep. Supplementation of the diet with a suitable source of the required element can prevent disease but such supplementation is often difficult, particularly when extensive systems of husbandry are being used. Other methods of supplementation, such as oral or parenteral doses which are many times the daily requirement involve risks of traumatic injury or inhalation pneumonia if solutions have to be administered by mouth, and the risk of toxicity due to the administration of large quantities of the trace element in a single dose.

These problems could be avoided if a depot of the trace element could be implanted at some site in the body from which it would be gradually released. An earlier paper (Allen et al., 1978) showed that depots of «controlled release glass» (CRG) not containing any particular trace element, dissolved at satisfactory rates when implanted subcutaneously behind the ears of calves. This paper describes observations in rats on the effects of subcutaneous implants of CRG, of a range of solubilities, containing copper.

Material and Methods

Glasses

Two series of 5 glasses (A and B) were used. They were both phosphate-based glasses, containing approximately 40% by weight of copper. Each series (A 1-5 and B 1-5) dissolved in water at 20 °C at rates of 1.0, 0.7, 0.4, 0.2 and 0.1 mg/cm²/hr, the rate of solution being proportional to surface area. The A series dissolved to give a solution of pH 4.0 and the B series to give a solution of pH 2.8. The glasses were formed into spherical pellets, approximately 2 mm in diameter, and weighed from 8-10 mg.

Rats

Ninety rats of the PVG/c strain were
used. They were housed in groups of three in polypropylene boxes and bedded on wood chips. Both before and during the experiment they were fed ad libitum with a diet* containing 15 mg/kg copper. Nine rats were implanted with each of the 10 formulations of glass. Before implantation each rat was anaesthetised with halothane (ICI) and prepared by shaving an area approximately 5 x 2.5 cm, about 2.5 cm posterior to the left forelimb. The area was swabbed with 70% alcohol and two previously weighed and sterilised pellets were implanted subcutaneously using an 11 gauge needle and stainless steel stilette. Each rat was examined daily for evidence of a clinical response and after 7, 14 and 21 days three rats implanted with each of the glasses were sacrificed. Blood samples were collected for copper estimation by atomic absorption spectrophotometry. The areas of implantation were excised and the glass pellets were removed, cleaned, dried and weighed.

Results

Table 1 shows the mean loss of weight from implants, in groups of three rats, of glasses A 1-5 (mean initial weight 18 mg) after 7, 14 and 21 days implantation. It also shows the mean copper concentration of blood samples taken when the implants were removed and a brief description of the reactions at the site of implantation. The solubilities of the glasses in vivo correlate well with their solubilities measured in vitro and vary from 5-25% of these values. The results obtained with glasses B 1-5 were similar except that, on average, slightly less glass dissolved from each type (5-10% of the in vitro solubility) and that the tissue reactions at the site of implantation were slightly more severe.

Discussion

The results shown in table 1 demonstrate that CRG's containing copper had two useful properties when they were implanted subcutaneously in rats. First, they dissolved at rates which were approximately proportional to their solubilities measured in vitro. Secondly, the increases in blood copper concentrations which were observed at intervals after implantation were approximately proportional to the rate of solution of the glasses; thus the copper released appears to be available for metabolic requirements. These two properties suggest that it should be possible to design CRG's with a variety of compositions and solubilities to provide the desired duration and rate of release of a selected trace element, for example, selenium, iron, manganese, molybdenum or iodine.

However, CRG's containing copper produ-

* LAD 1, Spratt's Patent Ltd., Barking, Essex.
ced tissue reactions which were more severe the more rapidly they released the element and the lower the pH of the resulting solutions. These reactions were presumably due mainly to the toxic effects of high local concentrations of copper, and were possibly exacerbated by low pH. Unless the reactions can be avoided, copper CRG’s cannot be applied practically. A possible method of reducing the reactions would be to implant them in a site with a more rapid flow of tissue fluids, in order to minimise the local concentrations of copper. When implanted intraperitoneally into rats, the CRG’s used in this experiment did not cause visible reactions, and experiments to test other more acceptable sites (eg. the neck) are in progress.

References
