Benzodiazepine Blockers

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Summary

Cytostatics are known to adversly effect the dosage scheme of many drugs.[1]

A case is described where the dosage of a benzodiazepine had to be multiplied six times to obtain a reliable sedative effect in a child on cytostatic treatment.

Introduction

C.P. a four year old girl weighing 14 kilogrammes (S.L.H. No. 243896) presented with anaemia and on full investigation on acute form of lymphoblastic leukaemia was diagnosed. She was started on Vincristine 1mg IV weekly. Prednisone 80mg and Ampicillin 500mg daily by mouth. The child did not respond but developed epileptiform convulsions and an EEG showed generalised showery periodic high amplitude waves that could not be traced to a particular focus even though a CAT scan was performed. Accordingly Asparginase 3000 units IV weekly was added to the above therapy. Advice was sought from the consultant staff of the Royal Marsden Hospital and Methotrexate 6.5 mg intra thecally weekly was added to the above drug regimen.

For sedation prior to lumbar puncture Trimeperazine Tartarate (Vallergan) syrup in 60mg dosage was used with good effect every week. Still the child failed to improve and cranial irradiation was recommended by the London consultant at 1800c range each every week for three doses at weekly intervals.

To enable good alignment for radiotherapy it was demanded that the child's head be fixed and immobile during the few minutes of irradiation. Anaesthetic advice was sought for the heavy sedation required for the procedure of radiotherapy. Diazepan (Valium) 2mg and Trimeperazine Tartarate (Vallergan) syrup 10mg by mouth were given but the child could hardly be controlled and objected to head fixing and even after Pethidine 50mg was given slowly IV the child moved. The first attempt at radiotherapy was postponed. After a week a benzodiazepine Fluonitrazepam (Rohypnol) (0.1 mg per kg body weight) was chosen and 2mg by IV route given – the dosage calculated to be enough for the 14kg child. The effect was negligible and so additional doses were given IV to a total dose of 8mg until some degree of drowsiness was arrived at and adequate head fixation for the child could be effectively organised.

There was no loss of muscle power or any tidal volume deficit during the 15 minute period the child was asleep and when she woke up she was fully active and playful. Investigations carried out at the time showed a Hb of 11.5gm./Wbc 3000/1 cmm. PCV 35%. Platlets 17,000/1 cmm. The uric acid was 8.5 mg per 100 ml and the ESR 110 mm in 1 hour. Differential blood smear showed 56% lymphoblast count and the bone marrow contained 95% immature lymphoblasts. The liver function test showed a raised alkaline phosphatase 571 ITU and the plasma protein 5.7 mg per 100 ml with high globulin ratio.

Discussion

It is not fully appreciated that many cancer patients on high doses of cytostatic agents may react adversly to drugs given in the usually recommended doses.

This case illustrate an abnormal reaction to the benzodiazepine. No other side effect to this drug was encountered despite the high dosage used.

Respiration was not embarassed, the blood parameters remained normal and the child had no hangover. It is interesting to note that when another anaesthetist was called to sedate the child for radiotherapy in the following week he decided to try Ketamine (Ketalar) and gave 14 mg IV the usual dose of the drug at 1 mg per 1 kg IV and obtained sufficient sedation to enable radiotherapy to be carried out.

According to the dose response curve in man higher doses of benzodiazepine do not increase the immediate hypnotic effect but probably the period of sedation or drowsiness. This case was exceptional in that after the short sleep the child awoke refreshed and playful.[2]

Conclusion

Benzodiazepines are known to increase the sedative effect of GABA in the brain but the use of cytotoxic agents appear to reverse this effect.

The problem of plasma protein changes due to

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the leukaemic process disturbing drug ionisation cannot be supported, as the other non-benzodiazepine drugs worked satisfactorily.

A lacuna of knowledge on the effect of cytostatic agent on brain enzymes exists and further experiments are needed to elucidate the site of block.

References

1. **Steward D.J.** Manual of Paediatric Anaesthesia 2nd Edition p 97, (Churchill Livingstone 1985).
2. **Bruppacher R., Arend J.** Hoffman la Roche and Co. Limited Basle Switzerland p.c.