Impaired nitrazepam metabolism in hypothyroidism

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Summary

Delayed metabolism of a number of drugs has been described in hypothyroid patients. We report an elderly hypothyroid female who had prolonged delay in the metabolism of a commonly-used sedative, nitrazepam, and discuss the importance of delayed drug metabolism in hypothyroidism.

KEY WORDS: psychosis, nitrazepam, hypothyroid coma.

Introduction

Nitrazepam is frequently used for sedation in elderly patients, some of whom may be particularly sensitive to its central effects. There have been no previous reports of delayed metabolism of nitrazepam in association with hypothyroidism. The following case report illustrates such a delay and also demonstrates some of the atypical features of hypothyroidism at presentation in elderly subjects.

Case report

An 87-year-old widow presented in coma. The patient’s daughter gave a history that until a year before admission her mother was well, independent and living alone. During the ensuing year she became increasingly confused, depressed and very agitated and over the last 6 weeks she had developed urinary incontinence and disturbing visual hallucinations. Because of these psychotic symptoms she was given 5 mg nitrazepam which had been prescribed for her daughter-in-law. She fell asleep and remained unrousable until her admission 48 hr later. There was no history of alcohol excess or liver disease.

On examination she responded to painful stimuli with eye blinking only. The rectal temperature was 34·5°C. Her skin was pale and dry and she was almost totally bald. No goitre was palpable. The blood pressure was 110/60 mmHg, the apex beat was 58 beats per min and there was no evidence of heart failure or pulmonary disease. There was no hepatomegaly or stigmata of chronic liver disease. The relaxation phase of the biceps reflex was delayed. Both knee and ankle reflexes were absent. Plantar responses were flexor.

Routine haematology, plasma urea and electrolytes and liver function tests were normal. Serum tri-iodothyronine was less than 1 nmol/l (normal range 1·5–3·1 nmol/l), serum thyroxine was less than 30 nmol/l (normal range 71–148 nmol/l), the free thyroxine index was less than 1·9 (normal range 45–160) and serum thyroid stimulating hormone was greater than 25 mu/l (normal range less than 4·6 mu/l). Plasma cortisol was normal and plasma cholesterol was greater than 12 mmol/l (normal range 4·0–6·5 mmol/l). The electrocardiogram showed a generalized low voltage and sinus bradycardia.

The serum nitrazepam level taken 48 hr after ingestion was 95 ng/ml and remained practically unchanged 5 days later (Fig. 1). The level was 15 ng/ml on day 16. The patient made a good recovery with replacement therapy and was discharged home 7 weeks later.

Discussion

The absolute bioavailability of nitrazepam given orally has been determined by using 14C nitrazepam. A wide inter-individual variation was observed, ranging from 54 to 93%. The fraction of nitrazepam
The delayed hepatic metabolism of other compounds such as antipyrine and propranolol in hypothyroidism has been previously documented (Shenfield, 1981) and we believe that the sustained elevation of plasma levels in this patient was caused by similarly delayed metabolism which has not been previously documented for nitrazepam or other agents metabolized by reduction and acetylation reactions. It is important to bear in mind the influence that hypothyroidism can have on drug metabolism and therefore the added influence of sustained raised circulating levels of some drugs such as sedatives and tranquilizers, on altered levels of consciousness associated with hypothyroidism. Drugs may precipitate the onset and prolong the duration of altered levels of consciousness in hypothyroid patients (Impallomeni, 1980).

Furthermore, this case illustrates that hypothyroidism may present with frank psychotic features; this is particularly true of elderly patients. From a series of 2,000 consecutive admissions to an acute geriatric unit the incidence of hypothyroidism was 2.3%. Less than a third of these cases demonstrated classical signs and symptoms of hypothyroidism but 22% presented with psychotic symptoms. The majority had depression and the remainder had paranoid symptoms similar to the presentation of our patient (Bahemuka and Hodkinson, 1975).

In summary, we have described a marked delay in nitrazepam metabolism in an elderly hypothyroid patient, together with the clinical implications of delayed drug metabolism in hypothyroidism and the frequently atypical presentation of hypothyroidism in elderly patients.

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References

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