ADVANCES IN IMMUNOPHARMACOLOGY 2

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Phenytoin and Humoral Immunity: Background and a Pharmacokinetic Interpretation of Recent Findings

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ABSTRACT

A number of reports have demonstrated that phenytoin may alter humoral immune function. After a brief review of some of the reported findings, we present our own observations of the effects of both phenytoin and its major metabolite, 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH) in mice. In vitro pre-incubation of mice spleen cells with phenytoin (10, 20, 50mg/L) but not HPPH, was found to increase the number of plaque forming cells (Jerne plaque assay). In vivo, however, both compounds upon repeated dosing for 3 and 7 weeks, appear to be immunosuppressive as determined using this assay system. At the highest dose (50mg/kg) schedule studied, however, phenytoin demonstrated great variation in its effects.

It is suggested that phenytoin per se may be immune-enhancing whereas, its metabolite(s) is immunosuppressive. If this assumption is valid, then the variation in phenytoin's effects on humoral immunity at high doses may be explained by the known unique nonlinear pharmacokinetic characteristics of this drug.

KEYWORDS

Phenytoin; 5-(p-hydroxyphenyl)-5-phenylhydantoin; humoral immunity; plaque forming cells; pharmacokinetics; nonlinear kinetics; immunosuppression.

INTRODUCTION

Although phenytoin (diphenylhydantoin; Figure 1) is widely recognized as a safe and effective drug in the treatment of major epilepsy, there are a number of reports indicating that this agent may be associated with immunological changes in epileptic patients and experimental animals. (MacKinney and Booker, 1972; Sorrell and Forbes, 1975; Seager, et al, 1975; Levo, et al, 1975; Bluming, et al, 1976; Fontana, et al, 1976; Fossan, 1977; Hornby and Mullen, 1977; Queiroz and Mullen, 1980; Thatcher, et al, 1982; Dosch, et al, 1982; Gilhus, et al, 1982; Gilhus, 1983). Phenytion has been extensively studied but is not unique in this regard since other anti-epileptic drugs also appear to be capable of causing immunological changes (Sorrell and Forbes, 1975; Queiroz and Mullen, 1980; Gilhus, et al, 1982).

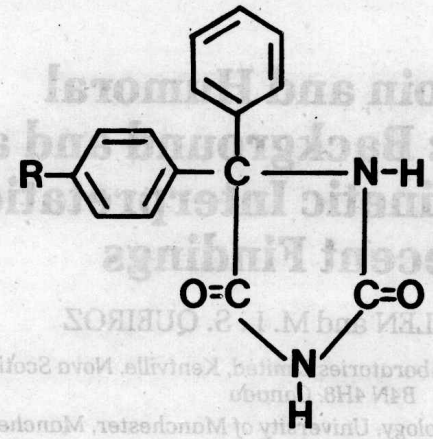

Fig. 1 The structure of phenytoin (diphenylhydantoin; R=H) and its major metabolite 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH; R=OH).

HUMAN STUDIES

Phenytoin has been shown: to induce a lymphopenia at high serum concentrations (MacKinney and Booker, 1972); to reduce *in vitro* lymphocyte responses to the (T-cell) mitogen phytohaemagglutinin (Sorrell and Forbes, 1975; Thatcher, *et al*, 1982) and the mixed-lymphocyte culture reaction (Bluming, *et al*, 1976); to lower serum and salivary IgA levels (Seager, *et al*, 1975; Fontana, *et al*, 1976), an observation occuring with greater frequency in patients possessing the HLA-A_2 antigen (Gilhus, *et al*, 1982); to reduce the number of cells forming "E rosettes" following *in vitro* exposure (Hornby and Mullen, 1977; Gilhus, 1983); and, rarely, to be associated with certain lymphoproliferative disorders (Lapes, *et al*, 1976). Recently, Dosch and coworkers (1982), reported abnormal suppressor T-cell activity concomitant with hypogammaglobulinemia in a child who had developed a pronounced generalized edema, rash and lymphadenopathy while receiving phenytoin for one year.

ANIMAL STUDIES

In mice, orally administered (two months) phenytoin was found to produce distinct histological changes in various lymphoid tissues (Kruger, 1970).

Levo, *et al*, (1975) reported that daily subcutaneous injection of phenytoin (500 µg per mouse) for periods up to 14 days did not affect Concanavalin A-induced transformation of spleen cells, although absolute spleen cell numbers were reduced. These workers also noted that subcutaneously administered phenytoin caused a significant reduction in humoral immunity as detected using the plaque-forming cell assay technique (Jerne, *et al*, 1963). Interestingly, phenytoin also afforded protection against urethane induced lung adenomas. On the basis of their findings, Levo, *et al*, (1975) concluded that in mice, phenytoin depressed mainly humoral immune function, which was in turn, somehow (decrease in blocking factors?) capable of providing protection against urethane-induced tumors.