

March 2, 2012

Dear Editor,

**Comment [Editor1]:** Please enter the date of submission here.

**Comment [Editor2]:** Please enter the name of the editor-in-chief of your target journal here.

Please find enclosed our manuscript titled “Valproic acid-induced fatal hepatotoxicity in infants: a report of 3 cases” as a Case Report for publication in *Journal of Internal Medicine*.

Hepatic failure resulting in fatalities has been reported in children receiving valproic acid and its derivatives. Research has indicated that infants are at a considerable increased risk of developing fatal hepatotoxicity. Hepatotoxicity cases are still reported in Japan, but there are no recent data. We conducted a retrospective study to clarify the epidemiology of fatal hepatotoxicity in recent years in Japan. Data was collected from 123 patients through a questionnaire survey. The incidence of hepatotoxicity was approximately 0.02 cases per million per year during the 10 years from 2001 to 2010. Children on multiple anticonvulsants, those with congenital metabolic disorders, and those with organic brain disease showed a high incidence of fatal hepatotoxicity. Children under 6 months of age showed earlier onset of hepatotoxicity. Therefore, when valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent.

We believe these findings are of particular interest to the readers of *Journal of Internal Medicine* because they describe the recent trend of hepatotoxicity in Japan and also identify children on multiple anticonvulsants, those with congenital metabolic disorders, and those with organic brain disease as a group with higher disease risk.

This manuscript has not been published and is not under consideration for publication elsewhere. The authors report no conflicts of interest. The manuscript has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing papers written by scientists whose native language is not English.

We appreciate your review of this manuscript for publication in *Journal of Internal Medicine*.

Sincerely,

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