Prions, urinary gonadotrophins and recombinant gonadotrophins

Dear Sir,

The lack of reported cases of variant Creutzfeldt-Jakob disease (vCJD) associated with urinary gonadotrophins is not a proof of their safety. One should bear in mind that vCJD incidence is $1 \times 10^6$ (at any one point in time), which translates to a lifetime risk of $1 \times 10^4$. On the other hand vCJD was first described in 1996 (Will et al., 1996), whereas the incubation period, until clinical signs become evident, ranges from 1–11 years. Animal studies indicate that the incubation period is linked both to the dose and to the route of exposure. The lower the dose, the longer the incubation period (Ricketts et al., 1997). Second, the more peripheral the inoculation, the longer the incubation period (Brown, 1994). Moreover, as far as we know, the history of gonadotrophin exposure has not been systematically investigated among vCJD patients.

By 1985, a series of case reports in the USA showed that, when injected, cadaver-extracted pituitary human growth hormone could transmit CJD to humans (Centers for Disease Control, 1985). Shortly thereafter, it was recognized that cadaver-extracted human gonadotrophin administered by injection could also transmit CJD from person to person (Cochius et al., 1992). In such cases where the agent entry to the brain was haematogenous, the mean incubation period was 12–13 years (range 5–30) (Brown et al., 1996).

We agree that the risk of vCJD transmission associated with urinary gonadotrophins is theoretical, and if any, probably very rare. However, the work of Shaked et al. (2001), identifying prions in the urine, raises some reasonable doubt and concern. Such uncertainty cannot be resolved until the following issues have been addressed: (i) systematic search of a history of urinary gonadotrophins among patients with vCJD and (ii) investigation of the effect of the extraction of urinary gonadotrophin when applied in urine of vCJD patients.

However, the question raised by Jansen (2003) is of interest, since it highlighted that recombinant gonadotrophins are not completely risk-free since in their manufacturing process bovine fetal serum is used, as well as monoclonal antibodies. We agree that recombinant gonadotrophins are not absolutely risk-free, but the use of source of materials from countries which have no reported cases of bovine spongiform encephalopathy (BSE), minimizes the risk. On the other hand, the use of fetuses as source reduces still more that risk, since the accumulation of transmissible spongiform encephalopathy infectivity occurs over an incubation period (European Agency for the Evaluation of Medicinal Products, 2001).

In any event, we think that the implementation of the two aforementioned recommendations (search of history of gonadotrophin exposure and investigation of the manufacturing process when contaminated products are used) should also be performed in the case of recombinant gonadotrophins. Risk assessments need to be conducted in both blood- and urine-derived gonadotrophins to determine the actual likelihood of transmitting infection in ovarian stimulation protocols (Reichl et al., 2002). On the other hand, as the European Agency for the Evaluation of Medicinal Products says: manufacturers are encouraged to continue their investigations into removal and inactivation methods to identify steps/processes which could have benefit in assuring the removal or inactivation of transmissible spongiform encephalopathy agents (European Agency for the Evaluation of Medicinal Products, 2001).

Until such questions have been answered or more additional scientific information is available, we would discourage the use of urinary gonadotrophins, if their sources are not BSE-free countries. Recently introduced highly purified menotrophins, not commercially available in our country when our first Letter to the Editor was written (Matorras and Rodriguez-Escudero, 2002) are extracted from the urine of postmenopausal women from Argentina, a low-risk country for BSE and CJD. Thus they seem also to be an acceptable option.

References


Letters to the Editor


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