Letters to the Editors

Ventricular arrhythmias and nonsedating antihistamines

De Abajo & Rodriguez carried out a cohort study with a nested-case control analysis to assess and quantify the risk of ventricular dysrhythmia associated with the use of five nonsedating antihistamine drugs [1]. Two observations from this study merit further discussion. First, although the study reports a low incidence rate of such events (1.9/10 000 patient/years; 95%CI: 1.0–3.6) after nonsedating antihistamine use, this rate is surprisingly four times higher than the rate during nonuse. Second, the relative risk (RR) observed for terfenadine (RR = 2.0) is remarkably low when compared with astemizole (RR = 17.8) or cetirizine (RR = 7.1). This is somewhat unexpected since previous large-scale epidemiological studies found that terfenadine users had risks similar to that of users of sedating antihistamines and ibuprofen [2, 3], while an analysis of WHO spontaneous adverse drug reports suggested that terfenadine may carry similar or larger risks of serious ventricular dysrhythmia than other antihistamines [4]. These unusual findings may be related to unidentified methodological limitations of the study design that could have biased the estimates.

First, depletion of susceptibles may have occurred because the reference group of 'non use' was formed with the time period *following* the use of nonsedating antihistamine drugs. Thus, because only the first ventricular dysrhythmia event was considered, subjects for whom this cardiac event occurred during the initial drug exposure were ineligible for inclusion in the reference 'nonuse' group, which was thereby depleted of these possibly high-risk subjects. Consequently, if some subjects were more susceptible to develop ventricular dysrhythmias, the study design forced them into the exposed group. This will necessarily underestimate the incidence rate in the nonuse reference group, thereby artificially increasing the overall RR and the RR for individual nonsedating antihistamines.

Second, since terfenadine prescriptions decreased by 52% during the follow-up period (Jan 92-Sept 96), major changes in prescribing habits were taking place. This figure suggests that a large number of subjects initially started on terfenadine were switched to other agents sometime during the follow-up period. If the reason for switching was related to the risk of ventricular dysrhythmias, with switchers being more at risk, disproportionately higher relative risks will be observed with other agents.

Finally, it was noted that total prescriptions of nonsedating antihistamines decreased roughly from 10 000 to 7000 per month. Thus, we can deduce that the use of nonprescription antihistamine drugs during the follow-up period, which was not considered in the study, may have been increasing to compensate the decrease in prescriptions. Consequently, the rate of ventricular dysrhythmia in the reference 'nonuse' group will likely increase over the span of the study. Whether this phenomenon affects the rate ratios in any way was not assessed.

Based on these limitations in study design and data analysis, the relative risks reported (1) may be biased. Any future epidemiological study conducted to confirm these findings should: (1) include a concurrent reference group composed of genuine nonusers of nonsedating antihistamines, (2) assess whether depletion of susceptibles was present, (3) consider changes in prescription patterns over time in the data analysis and (4) assess the effect of calendar time when estimating the relative risks to account, at least in part, for time trends in the unavailable nonprescription exposures.

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Reply

Suissa makes some criticisms on our paper and we would like to comment on them. He claims that our results are 'unusual' because they are consistent neither with two previous epidemiological studies nor with the analysis made by the WHO Collaborative Centre based on spontaneous reports. His interpretation is puzzling as he omitted to mention in his letter that the estimates for individual antihistimanics were based on very small number of cases, and consequently all estimates of relative risk were overlapping. We commented extensively on these three papers in our manuscript, and concluded that our findings were consistent with their results and others, despite important methological differences and supported the hypothesis that the risk of ventricular arrhythmia associated with terfenadine in the population at large was not materially different from the one presented with other antihistamines as a group.

Suissa raised some interested methological issues. Following his suggestions we have re-examined our data searching for any evidence supporting the various potential biases he postulated. First, 'depletion of susceptibles' may certainly be a theoretical source of bias when only first events are considered; however, in our study, all nine cases with a ventricular arrhythmia episode during current use of antihistamines did not present any other new episode after the first one during an average follow-up of 4 years after the index episode, irrespective of exposure status. Second, Suissa argues that the increased risk observed with non-sedating antihistamines other than terfenadine can be explained if patients at higher risk of ventricular arrhythmia have been switched from terfenadine to these other antihistamines; nevertheless, our data indicate that none of the six cases who were current users of other non-sedating antihistamines were past users of terfenadine. Finally, Suissa contends that the decreasing use of non-sedating antihistamines over the study period may have increased the rate of ventricular arrhythmia among non-users, as an increasing number of them may have actually become users of OTC antihistamines; again this speculation is not consistent with our data: the rate of ventricular arrhythmia among non-users was one per 17 000 person-years over the period 1992–93 and one per 28 000 person-years over the period 1994–96, a trend in the opposite direction predicted by Suissa.

In conclusion, we were not able to substantiate empirically any of the limitations pointed out by Suissa, which, we assume, reinforces the validity of our results.

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Binding of propofol to blood components

Apart from a misleading title, there are some methodological flaws worth commenting upon, in the work presented by Mazoit & Samii [1]. Our group has been researching and reporting on the binding properties of propofol for several years. We also have experience in pharmacokinetics/pharmacodynamics. The part of the title making reference to that field is inappropriate since the work presented was *in vitro,* on isolated proteins. Only in the discussion section there is a general mention of the implications that changes in the free fraction of a drug can have on pharmacokinetics and pharmacodynamics. We think scientific article titles (also keywords) should represent faithfully the true contents of the original research, not that of implied knowledge, and should be more carefully selected. Further, it is known that propofol adsorption to membranes has a time dependence demostrated by validated techniques (5 min centrifugation at 37 ° C) [2–4]. In reference to the methodology of Mazoit & Samii on page 36, they are vague when mentioning that '...(found) an adsorption $\geq 20\%$ on the dialysis and ultrafiltration membranes tested depending on the material and the membrane cut-off'. Then, discarding the established technique, they proceed to employ an alternative. In this instance, the authors fail to specify the conditions leading to their results (time or cut-off of their membrane system) and hence to justify their method. We certainly agree with the fact that propofol binds to human serum albumin (HSA). We have published similar results in isolated HSA [5]. But, in later reports we point out that this appears to be so when albumin is the *only* protein present [2–4]. So, in another study with serum from critically ill patients with very reduced albumin count ($16.3\,g\,l^{-1}$ *vs* $45.8\,g\,l^{-1}$ in healthy controls), this protein only accounted for 25% of the minor changes observed in the overall binding of propofol [3]. Furthermore, in patients with hepatic deficiency and significantly reduced albumin levels with respect to healthy volunteers ($35.39\,g\,l^{-1}$ *vs* $50.85\,g\,l^{-1}$), the binding of propofol was not altered [2]. In view of our results with patients we performed a study on isolated lipoproteins from human serum [4]. In this study the lipoprotein fractions were isolated by density gradient ultracentrifugation [6] because the fractions purchased from Sigma Chemical (as in the work of Mazoit & Samii) did not bind propofol. We found that binding was 88% to VLDL, 93% to LDL and 91% to HDL when *physiological* concentrations of these proteins were employed. Additionally, when we used serum extracted from hyperlipidaemic patients we found that the unbound fraction was significantly diminished with respect to healthy individuals. Regression analysis also showed that there was significant correlation between the bound-to-free ratio of propofol and lipoprotein levels

whereas albumin and α_1-acid glycoprotein proved irrelevant [4]. Further work performed by our group involving patients with altered lipoprotein count also indicate that lipoproteins and not albumin (as is suggested by Mazoit & Samii) are the principal components affecting propofol binding in serum.

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Reply

We have read with great interest the letter from Suarez *et al.* [1]. Unfortunately, when we submitted our article, the most recent article from their group [2] was not yet published and we were unable to incorporate their results to our discussion. Their letter gives us the opportunity to improve the discussion on the points raised by their paper.

We do not agree with the statement that the tittle of our paper is misleading. It is no more misleading than the tittles from their previous papers [2–4] and we think that the words 'implications for PK-PD' are no more misleading than the word 'significance' used by Zamacona *et al.* [2]. We measured propofol binding to serum drawn from volunteers and to isolated proteins exactly as did these authors. We also measured propofol binding to red blood cells which appeared to bind half the propofol molecules in blood as it was previously shown [5].

We agree that propofol adsorption is time dependent and, because we never have been able to perform ultrafiltration in less than 15 min (total time between pipetting into the device and ultrafiltrate sampling) we used an alternative method. In fact, we tested different membranes including YMT membranes (the same as those used in the MPS1 system). In our lab, the latter membranes exhibited more than 20% binding after 30 min incubation.

In a study done in patients with a reduced albumin content, Suarez *et al.* found a 25% decrease in propofol binding [4]. This decrease is in accordance to our predictions from *in vitro* binding measurements. We totally agree with Suarez *et al.* when they state that propofol do not bind to the proteinic part of the lipoproteins. They used ultracentrifugation, which permits to obtain proteins in their integrity. However, these proteins are surrounded by their natural environment, which is lipidic in essence in the case of lipoproteins. However, the discrepancies between their results and ours may be explained by the fact that propofol is highly soluble in lipids. Therefore, propofol is not only bound to the lipidic part of lipoproteins but also propofol is solubilized by the lipids carried by these proteins. Moreover, because propofol is used as an emulsion in Intralipid®, this carrier system may represent a major component of transport. Then, the two approaches used by Suarez *et al.* on one hand, and by us on another hand, are complementary and allow to better understanding the process of binding and transport of propofol in blood.

In conclusion, we continue to assert that the first site for propofol binding in blood is the red cells. However, anaemia per se is unlikely to induce an increase in propofol free fraction. Conversely, hypoalbuminemia would have more important effects on binding. We missed the role of lipids in propofol transport, and Suarez *et al.* indirectly pointed out that effect. The carrier lipidic emulsion is certainly of major importance, especially in patients receiving long-term infusion for sedation. This factor remains to be studied.

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