

Response to a letter to the editor by Satvika Uppu

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Linked Article

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With this letter, we would like to respond to a letter to the Editor by Miss Satvika Uppu (Uppu, 2013). In her letter, Uppu presents some old literature on 2-aminoethyl nitrate (AEN) that we missed to cite in our previous published work by Schuhmacher *et al.*, (2009). Although, we are indebted to Miss Uppu for bringing this information to our knowledge, we would like to defend ourselves against the impression conveyed by her that it was our intention to conceal these older literature to the readers of the *British Journal of Pharmacology*. We have screened the PubMed database for older life science literature on this compound and used the correct search term '2- aminoethyl nitrate' (chemically correct IUPAC nomenclature) producing meanwhile 37 hits in the PubMed database. However, none of these publications was associated with the compound of interest. Using the search term 'aminoethyl nitrate' brings up our own publication by Schuhmacher *et al.*, (2009) and the editorial on it by Bauersachs, (2009). Using the search term '2-Nitrooxyethylammoniumnitrate' produces two hits by Lehmann and coworkers (Koenig *et al.*, 2007; Roegler *et al.*, 2010), our co-authors on the work by Schuhmacher *et al.* who provided the aminoethyl nitrate compound and also described the synthesis in detail (obviously these publications were not found by Miss Uppu). Finally, using the chemically incorrect search term 'aminoethylnitrate' brings up two older clinical studies on this drug (Ehrenberger, 1960; Batterman and Mouratoff, 1963) and a newer one on a aminoethyl nitrate hybrid molecule (Abe *et al.*, 2003). Another chemically incorrect search term '2-aminoethyl-nitrate p-toluenesulfonate' (but only when added exactly like this! Omitting 'p-toluenesulfonate' from the search term will produce no hit) yielded another publication by Kinnard and colleagues (Kinnard *et al.*, 1964). Learning the trademark names of AEN, 'itramintosylate' or 'Nilatil', from these previous studies, even revealed four more published studies in PubMed (Soderstrom, 1958; Ejrup and Kumlin, 1961; Fremont, 1967; Takenaka and Umeda, 1976). Therefore, knowing the different (in some cases incorrect) chemical and trademark names of a given drug will make it easy to dig out some older literature on it. However, authors are not committed to search for chemically incorrect drug names such as 'aminoethylnitrate'.

However, as pointed out at the beginning of this response, we are thankful to Miss Uppu for bringing this information to us and to the readers of *British Journal of Pharmacology*. We would like to take the opportunity to add some more information on these old studies and the history of aminoethyl nitrate (2-nitrooxyethylammoniumnitrate,

aminoethylnitrate, 2-aminoethyl-nitratetoluenesulfonate, itramin tosylate). Obviously, this nitrate was on the market from 1957 to 1969 not only in Sweden but also other European countries and distributed by the company Pharmacia. The drug safety was based on toxicology studies in rats revealing a quite high and favourable LD50 >200 mg·kg⁻¹. Already in 1958, there is a published report by Söderström on the antianginal effects of aminoethyl nitrate (Söderström, 1958). The report by Söderström, although quite detailed and covering nine pages, is unfortunately written in Swedish and therefore only suitable for a limited group of readers. The clinical studies of Batterman *et al.* and Ehrenberger demonstrated in 18 or 12 patients that the 4 × 4 mg or 3 × 2mg dose of AEN efficiently controlled angina pectoris with only minor side effects such as nausea and lightheadedness (Ehrenberger, 1960; Batterman and Mouratoff, 1963). It should be noted that each of these two reports covers 1.5 pages and therefore rather resemble a case report than a full research paper. More informative is the study by Fremont carried out in 29 patients with comparison of the antianginal effects of AEN to nitroglycerin covering 11.5 pages and providing all essential information on the study design, the used techniques and patient characteristics. Kinnard *et al.* performed pharmacokinetic studies in dogs providing detailed information on the methods, results and interpretation (Kinnard *et al.*, 1964). All of these previous studies that we could read measured effects of AEN versus nitroglycerin on blood pressure, coronary flow or more subjective parameters such as nausea, headache score or capacity (how many blocks can a patient walk until angina symptoms?). None of these studies addressed the results of our own report by Schuhmacher *et al.*, (2009): Comparison of AEN to nitroglycerin with respect to effects on endothelial function, *in vitro* and *in vivo* tolerance measured by tension recordings, assessment of the role of ALDH-2 for their bioactivation, investigations of the bioactivation pathway of AEN by inhibitors of signalling pathways, reactive oxygen species formation. Therefore, our work is still original and new but the title of our work and the main conclusion should have been rephrased in light of the older literature.

To summarize, we thank the Editor, Professor McGrath for his fair handling of this matter, and we would like to make clear that we published our work in the best knowledge that our data were original new findings.

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Corrigendum

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Since the publication of Schuhmacher *et al.*, (2009) the following correspondence has been published concerning changes in nomenclature affecting this paper: McGrath 2013; Uppu 2013; Daiber 2013.

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