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CORRESPONDENCE

Reply to "Unsettled issues regarding intensive insulin therapy in the intensive care unit"

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In response to the thoughts expressed by van Braam Houckgeest, Schultz and Spronk [1] et al after the editorial recently published in this journal [2], some issues require clarification. The opportunity to pursue the discussion, which started elsewhere, with the same discussants [3] is really appreciated.

The first clarification needed is the degree of achievement of the target blood glucose level in the "control" arm of the various studies quoted [4-10]. Even though the control target differed between studies, the mean morning blood glucose levels achieved ranged from 7.7 [4] to 9.5 [10] mmol/l [3]. In particular, the levels achieved in the control arm of the Leuven I trial [5] and of the NICE-SUGAR study [6] were very close 8.5 ± 1.8 and 8.1 ± 1.4 mmol/l, respectively. Therefore, the dramatic difference in outcome can hardly be attributed to the differences in targets of the control group, when the actual glycaemia was so similar. In respect to the mortality that was observed to be lower than expected in NICE-SUGAR, this is indeed intriguing. It is of interest that some investigations have already reported a "trial effect" that is reflected by better outcomes in patients included in interventional studies than in eligible but non-included subjects [11]. Likewise, in intensive care medicine, inclusion in a clinical research protocol was followed by an improvement in outcome (Annane et al unpublished).

Second, regarding the time to reach the target level, the interval between readings is obviously a key factor in the interpretation and comparison of data across different studies. Unfortunately, in the Leuven trials [6,7] only one value per day was available thus precluding any meaningful comparison with other studies which report the means of more frequent readings [4,5]. Nevertheless, the time to achieve the target range was particularly long in NICE-SUGAR [5], perhaps in relation to the inclusion criterion of an anticipated length of ICU stay of at least three days. Indeed, some time may have lapsed between the admission and an accurate prediction of the length of stay, thereby delaying the enrolment into the study by a few hours.

Third, the possibility of delayed toxicity related to the too-fast correction of hypoglycaemia is indeed an appealing research hypothesis which would need a formal assessment, probably requiring continuous or near-continuous intravascular monitoring in pre-clinical models.

The answer to the suggested alternative interpretation, the lack of external validity of the Leuven I study, is a strong incentive for the assessment of various degrees of glucose control in specific categories of patients, and new strategies (therapeutic algorithms, analysers, continuous monitoring), prior to any general recommendation.

Meanwhile; the principle of "*primum non nocere*" and the evidence now available are consistent with an intermediate glucose target, calculated to allow the avoidance of severe hypo- and hyperglycaemia. This target might differ from one setting to another and will change over time, but should be definitely selected as the safest and most effective available.

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