Investigations on Salicylate Protein Binding in Newborns and Infants

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Abstract. The non protein-bound portion of a drug is mainly responsible for the effect of a drug. If this free portion is changed for any reason, drug reactions varying from the normal may occur. Using sodium salicylate as an example, we have investigated this question in newborn children and in infants. It was shown that the newborns had significantly less salicylate protein-binding than the infants had. There was no significant difference of the binding constants between newborns with and without jaundice. In the 75 infants examined, 12 (15%) showed a significant reduction in salicylate protein-binding, but no definite relation to a specific disease could be established. A primary reduction in protein-binding, as well as a secondary reduction because of the disease, must be considered in these children.

The importance of this reduced protein-binding should not be underestimated. In patients with restricted renal function or lowered hepatic metabolic capacity, it may lead to a delayed excretion of the drug which has increased penetration into the tissues.

Key words: Protein-binding – Salicylate – Drug metabolism – Newborns.

Zusammenfassung. Die Wirkung eines Medikamentes ist unter anderem abhängig von dem freien, nicht proteingebundenen Anteil. Ändert sich dieser Anteil quantitativ, so können sich von der Norm abweichende Wirkungen einstellen. In Serumproben von neugeborenen Kindern und Säuglingen bestimmten wir die Proteinbindung von Na-Salicylat: Neugeborene wiesen eine signifikant niedrigere Proteinbindung auf als Säuglinge. Es bestand kein signifikanter Unterschied in den Bindungskonstanten bei ikterischen und nicht ikterischen Neugeborenen. Bei 75 untersuchten Säuglingen wiesen 15% (n = 12) eine signifikant geringere Salicylatbindung als der Durchschnitt dieser Altersklasse auf; eine Zuordnung zu bestimmten Krankheitsbildern gelang jedoch nicht. Es kann entweder eine primär geringere Proteinbindung oder eine im Rahmen einer Erkrankung sich sekundär verringeringe Protein-
The action of every drug is to some extent characterized by its pharmacokinetic properties, such as absorption, metabolism, excretion, distribution and protein-binding. The significance of the first four of these parameters is relatively clear, but many authors disagree about the effect of protein-binding on drug action. Protein-binding depends on the physico-chemical properties of a substance. Generally, the degree of binding is rather constant and hence demands no special attention in therapeutic considerations. The degree of protein-binding of a drug is usually unknown to the physician and this does not often appear to have any untoward consequences. There are, however, situations in which the protein-binding of a drug may change. For example, we know, from observations in adult patients that chronic liver diseases, and acute and chronic renal insufficiency, may reduce protein binding [1, 2, 3, 4, 7, 10, 11, 13, 20, 21, 22, 23, 24, 25, 26, 27, 30]. It is at present not known whether other diseases exert a similar effect.

It has further been shown that the protein-binding of many substances is much less in newborns than in older children or adults [5, 8, 9, 12, 14, 15, 18, 29, 32]. This is true of endogenous compounds such as bilirubin [34] and of exogenous substances, such as drugs. One of the causes of this phenomenon was thought to be the higher concentration of bilirubin in the serum of newborns, but the lower albumin concentration at this age has also been said to have an important effect [5, 15, 29].

In an earlier investigation, using sodium salicylate as an example, we found evidence that neither increased bilirubin levels nor lower albumin levels in the serum of newborns fully explained the lower degree of protein-binding [32]. In a further study, we have now investigated the questions of the reduction in protein-binding in newborns, and whether disease in children has any effect on protein-binding.

Material and Methods

We determined the binding of sodium salicylate in newborns and infants admitted to our hospital with various diseases. Only those children in whom an accurate medical history showed that no drugs had been administered during the 48 h before admission were admitted to the trial. The following groups were studied:

- Newborns, birth weight more than 2500 g (age 1—30 days), n = 33
  - total serum bilirubin below 12 mg/100 ml, n = 20;
  - total serum bilirubin over 12 mg/100 ml, n = 13;

- Infants aged between 2 and 17 months, n = 75.

The following conditions were present in the newborn children:
- Attacks of cyanosis
- perinatal complications (without intensive care treatment)
- hypoglycemia