

Laboratory stability testing to improve the safety of intravenous phenytoin use

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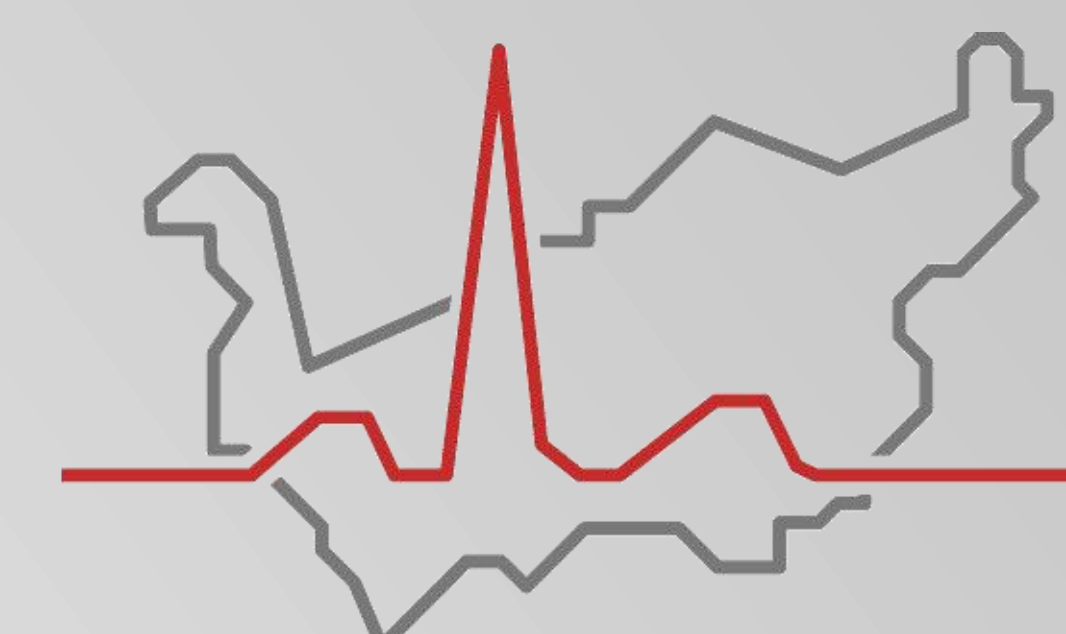
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Background and Objective :

Intravenous (IV) phenytoin is often used for the treatment of generalized convulsive seizures. Phenytoin stability requires a particular pharmaceutical formulation (pH 12) and adequate information to warrant its proper use (dilution and/or administration). In Switzerland, two different formulations of IV phenytoin (Phenhydan®) are available: the **buffered concentrate for infusion (CFI)** (750mg/50ml) (*fig.1*) that must be diluted, and the **unbuffered solution for direct injection (SDI)** (250mg/5ml) (*fig.2*) that must not be diluted. Despite many efforts to disseminate this information, those differences remain poorly known by nurses. Yet improper use can harm patients (venous thrombosis). The objective of this work was to improve the safety of the IV phenytoin use focusing on loading dose preparation.



Figure 1 – CFI



Figure 2 – SDI

Results :

For legal, logistical and economic reasons, import of fosphenytoin (not available in Switzerland) was abandoned. Furthermore the dose ratio between phenytoin and fosphenytoin (1:1,5) can lead to dosing errors. Sodium valproate use was also considered but lacks clinical evidence for this indication. The suppression of one of the two phenytoin formulations was also studied: using only SDI prevents a rapid administration of a loading dose when a central venous line is not available (too irritant) and using only CFI increases costs. A pharmacy-centralized production of bags containing loading doses as a substitution for CFI was considered but precludes any dose adjustment for weight and age.

Despite the manufacturer's recommendation, the additive compatibility of **3 SDI into 1 CFI diluted in 500 ml NaCl 0.9% (NS) or Dextrose 5% (D5)** was demonstrated in vitro (pH and concentration monitoring by HPLC) **without any precipitation or alteration of solution's stability during at least 24h at room temperature.**

Design :

Evaluation of alternate products or strategies and laboratory stability testing.

Setting :

Pharmacy and Intensive Care Unit of a tertiary care regional hospital.

Main outcome measures :

Feasibility and costs of each evaluated option.

pH (*fig.3*):

NS: 11.44 (start); 11.50 (24h)

D5: 10.53 (start); 10.50 (24h)

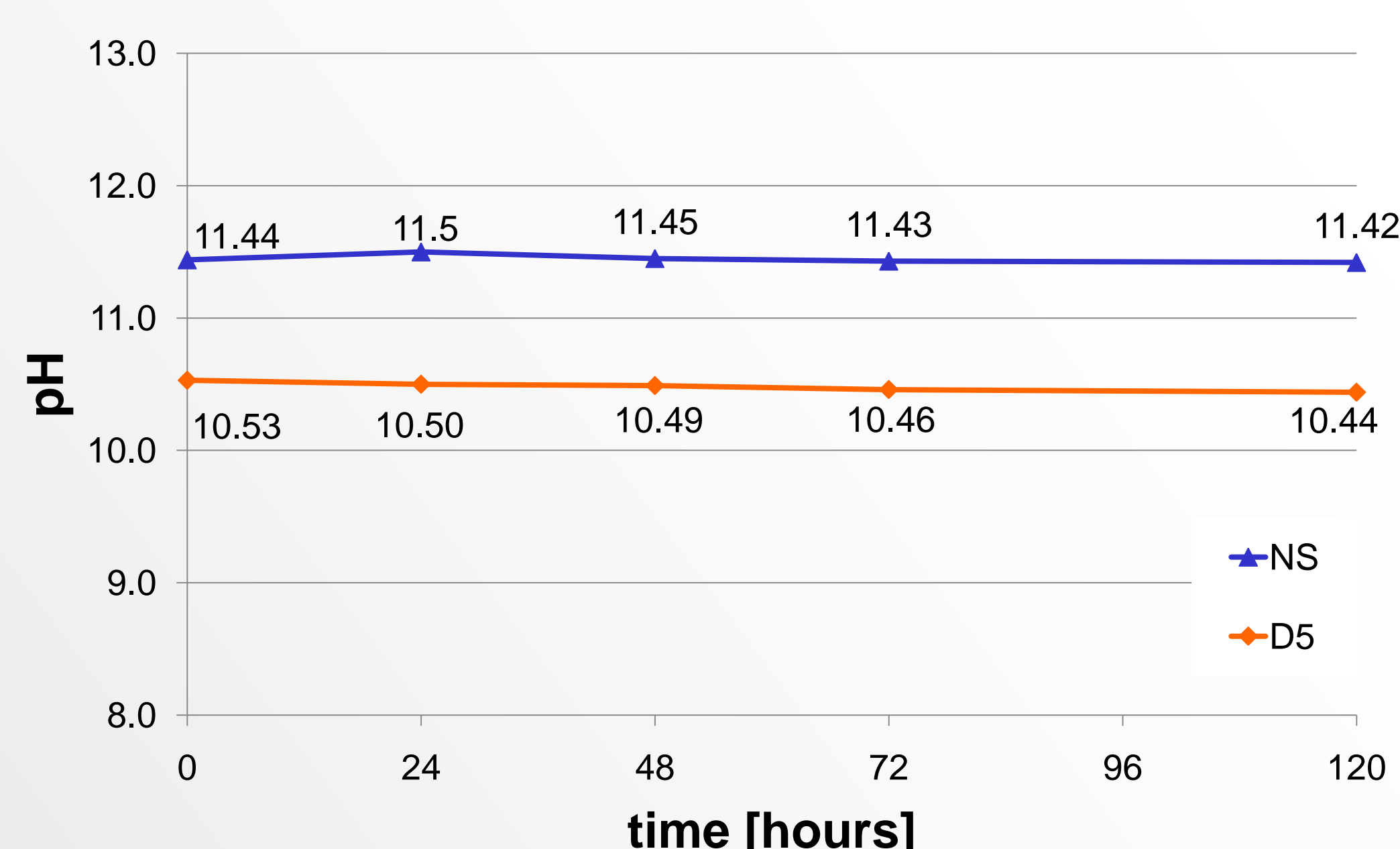


Figure 3 – Evolution of pH over time

Concentration (phenytoin) (*fig.4*) :

NS: 100.0% (start), 95.4% (24h)

D5: 100.0% (start), 101.9% (24h)

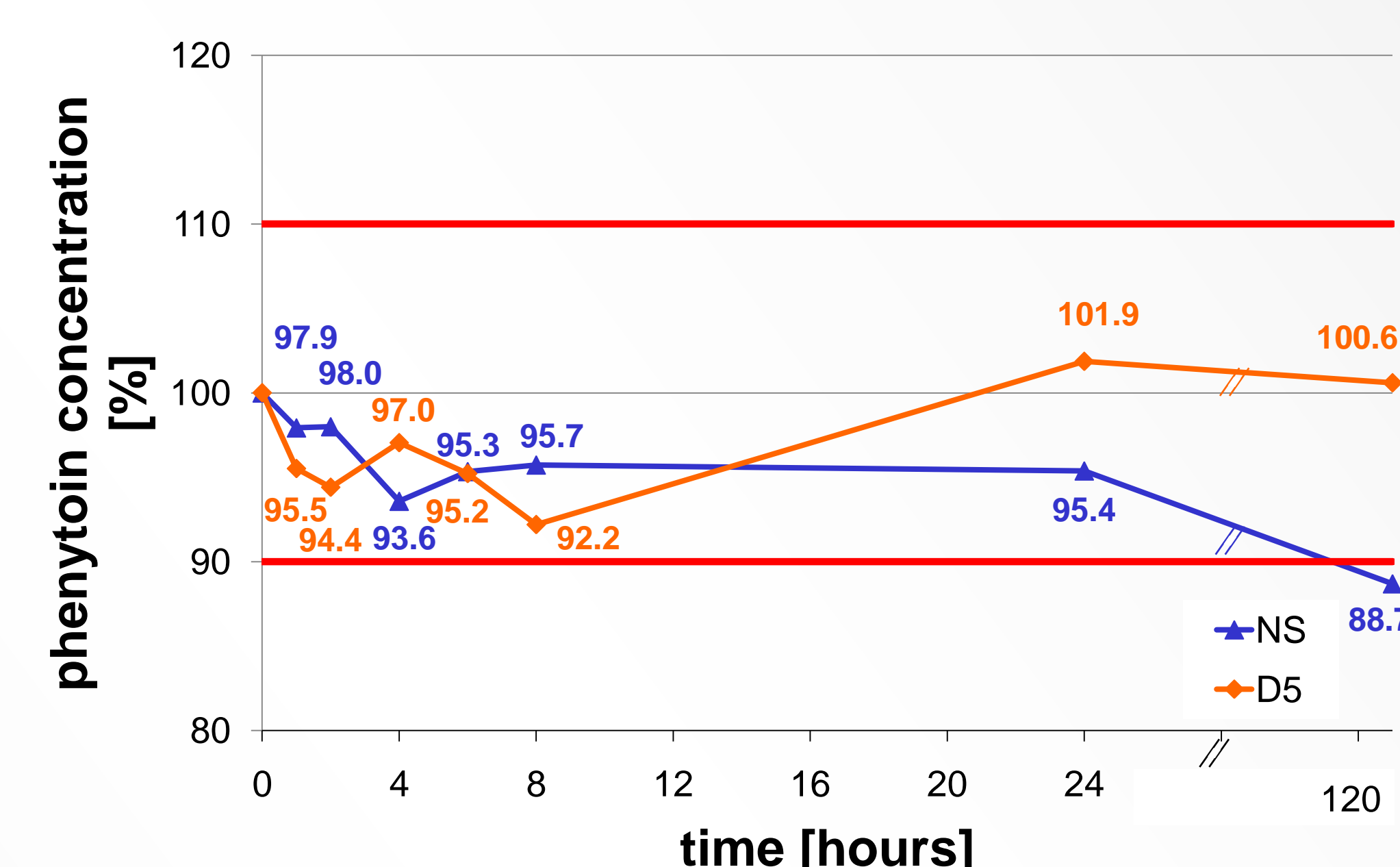


Figure 4 – Evolution of phenytoin concentration over time

Conclusions :

This evaluation involved many areas of the pharmacy: clinical pharmacy, logistics, compounding, laboratory and drug information. Even if communication remains a challenge, stability results allowed to simplify the message: **“To prepare loading doses, 1 to 3 SDI can be added to 1 CFI diluted with 500 ml of NS or D5”**. This information was disseminated to help nurses to improve the safety of IV phenytoin administration.