5 June 2022

GEDEFO-SEFH TECHNICAL NOTICE ON THE CHANGE IN THE DOSE EXPRESSION OF HYDROCORTISONE AND EQUIVALENCE IN INTRATHECAL PREPARATIONS

The Spanish Medicines and Healthcare Products Agency issued a technical notice with important information on drugs containing injectable hydrocortisone.1

The notice contains a list of medicines authorized in the Spanish market which contain different hydrocortisone salts as the active ingredient:

- Actocortina® 100 mg powder and solvent for solution for injection (Nr Reg. 28.824) (hydrosome sodium phosphate).
- Actocortina® 500 mg powder for solution for injection (Nr Reg. 52.105) (hydrocortisone sodium phosphate).
- Hidrocortisona Lorien 100 mg powder for solution for injection and for infusion (generic form) (Nr Reg.:86.292) (hydrocortisone sodium phosphate).

Exceptionally, in the event of a shortage, the drugs may be imported under the Exceptional Circumstances Authorization mechanism, of:

- Hidrocortisona Color 100 mg powder and solvent for solution for injection (hydrocortison succinate).

Until recently, dosages of the drug named Actocortina® were expressed as hydrocortisone salt rather than as hydrocortisone base as recommended by the current guidelines, unlike the recently approved Hidrocortisona Lorien and Hidrocortisona Color, imported under the exceptional ircumstances authorization mechanism.

To avoid dosing errors, this notice includes the table below, which specifies the amount of each salt contained in each of the medicines and their equivalence with respect to hydrocortisone base:

	Hydrocortisone base	Hydrocortisone sodium phosphate	Hydrocortisone sodium succinate	Reconstitution
Actocortina 100 mg powder and solvent for solution for injection (Nr Reg 28.824)	74,53 mg	100 mg	-	1 ml WFI
Actocortina 500 mg powder for solution for injection (Nr Reg 52.105)	372,65 mg	500 mg	-	5 ml WFI

Hidrocortisona Lorien 100 mg powder for solution for injection and infusion (generic form)(Nr Reg 86.292)	100 mg	-	133,7 mg	2 ml WFI
Hidrocortisona Color 100 mg/2ml powder and solvent for solution for injection	100 mg		133,7 mg	2 ml WFI

The Agency has announced that is has asked the manufacturer of Actocortina® to modify the said terms in the medicine's name and in the information on the product, which has already been included in CIMA:2

- Actocortina® 75 mg powder and solvent for solution for injection.
- Actocortina® 373 mg powder for solution for injection.

This entails a change in dosage form that could lead to dosing errors.

In the field of hemato-oncology, this change in the dosage form of Actocortina® and the coexistence of several hydrocortisone salts in the market have a specific impact on the formulation of intratheca therapies.

The use of triple intrathecal therapy (TIT) is not homogeneous and the TIT doses to be administered are not clearly defined, with significant variations between countries and/or research groups. The use of steroids combined with intrathecal chemotherapy is not universal, with significant variations in the steroids (dexamethasone, prednisolone, methylprednisolone, hydrocortisone) and in the doses used in the protocols of different research groups.3

In Spain, the most commonly steroid used in TIT is hydrocortisone. Although IT administration is not contemplated in the SmPC of the different medications, the IT route has become widespread in clinica practice. As stated above, the dosing of the drugs varies widely across different studies, as shown in the table below:3

Table 4. Dose of triple intrathecal chemotherapy (methotrexate, cytarabine and hydrocortisone) as a function of age

Study	Age	MTX dose (mg)	ARA-C dose (mg)	HC dose (mg)
Lin et al[12] & Liu et al[11]	<1 years 1.2 years 2.3 years >3 years	6 8 10 12	12 16 20 24	6 8 10 12
Franklin et al[24]	≤1 year 1.2 years 2.3 years 3-8 years 9 ≥years	7.5 8 10 12 15	15 16 20 24 30	7.5 8 10 12 15
Matloub et al[25]	<2 years 2-3 years 3-8 years >8 years	8 10 12 15	16 20 24 30	8 10 12 15
Mahoney et al[26]	1 years 2 years ≥3-8 years ≥9 years	8 10 12 15	16 20 24 30	8 10 12 15
Pui et al[65]	<2 years 2-3 years ≥3 years	8 10 12	24 30 36	16 20 24
Ortega et al[66]	<12 months 12-23 months 24-35 months ≥35 months	5 8 10 12	16 16 20 30	10 10 15 20
Ruggiero et al[79]	<2 years <3 years ≥3 years	8 10 12	16 20 24	8 10 12
Tomizawa et al[90]	<2 years <3 years ≥3 years	7.5 10 12.5	15 20 25	15 20 25
LAL SEHOP /PETHEMA 2023[81]	12-23 months 24-35 months ≥35 months	8 10 12	16 20 30	10 15 20
Ribera et al[82]	15-60 years	12	30	20

Not all the studies specify what hydrocortisone salt was used or whether the dosage refers to the hydrocortisone salt or the hydrocortisone base, which makes things even more uncertain. The salt marketed in the U.S.A. at the time was the sodium succinate, while in Spain the most frequently used salt until now has been the sodium phosphate. The dose equivalence between both salts is similar.

The PETHEMA and SEHOP, both of which include TIT, specify the following age-dependent doses of hydrocortisone:

- 20 mg in children older than 3 years and in adults
- 15 mg in children between 2 and 3 years
- 10 mg for children younger than 2 years

Although the protocols do not state whether these doses refer to salt or to base, in clinical practice doses have been expressed in sodium phosphate salts, with equivalences to hydrocortisone base being as follows:

- 20 mg of salt is equivalent to 15 mg of base
- 15 mg of salt is equivalent to 11 mg of base
- 10 mg of salt is equivalent to 7.5 mg of base

SEFH's GEDEFO-workgroup wishes to propose a strategy based on common criteria intended to prevent hydrocortisone dosing errors in TIT resulting from the aforementioned changes.

PROPOSAL BY SEFH'S GEDEFO GROUP

1.-To maintain the composition of TIT, changing the dose expression to hydrocortisone base and clarifying the equivalence with the previous salt-based dose:

- Hydrocortisone 15 mg (equivalent to 20 mg of sodium succinate/phosphate salt)
- Hydrocortisone 11 mg (equivalent to 15 mg of sodium succinate/phosphate salt)
- Hydrocortisone 7,5 mg (equivalent to 10 mg of sodium succinate/phosphate salt)

2.-To convey this information to scientific societies and institutions such as SEHH, SEHOP, SEOM, PETHEMA, etc., suggesting that, in order to avoid mistakes, the dose of hydrocortisone be expressed as a base, taking into consideration that up to now the drug was dosed as a salt and that the approximate equivalences between the two should be reflected in all newly-prepared protocols and in all revised versions of existing ones.

REFERENCES

1. Información relevante sobre los medicamentos que contienen hidrocortisona inyectable [Internet]. Agencia Española de Medicamentos y Productos Sanitarios. 2022 [citado 1 de junio de 2022]. Disponible en: https://www.sefh.es/fichadjuntos/MedicamentosHidrocortisona090522.pdf
2. **Fichas técnicas del Centro de Información online de Medicamentos de la AEMPS – CIMA** [base de datos en Internet]. Madrid, España: Agencia española de medicamentos y productos sanitarios (AEMPS) - [fecha de acceso junio 2022]. Disponible en: https://cima.aemps.es/cima/publico/lista.html
3. Olmos-Jiménez R, Espuny-Miró A, Cárceles-Rodríguez C, Díaz-Carrasco MS. Practical aspects of the use of intrathecal chemotherapy. Farm Hosp. 2017;41(1):105-129.