Monitoring of lamotrigine concentrations in five breastfed newborns

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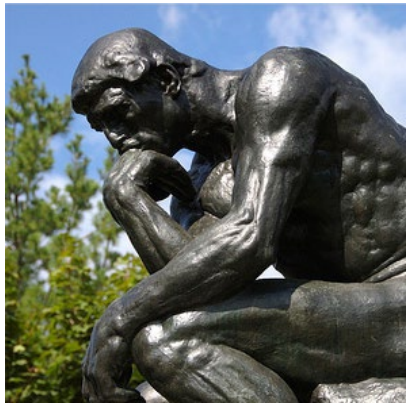
Lamotrigine and breast feeding : why are we still talking about this?



Rather numerous publications with dosages are trying to answer these questions

- Concentrations in breastmilk?
- Serum concentrations in infants?
- Correlation lamotrigine concentration in mother's serum and breastfed infant's serum?
- Risk for breastfed children?

Majority of results shows: substantial exposure for the breastfed child
inter-individual variability
relatively few adverse drug reaction but some serious ones

Main conclusions : possible breastfeeding with close monitoring (clinical and biological)

But increased requests by the medical staff
What to do in practice is difficult to define

The French Network of Pharmacovigilance Services

National level

National Agency for the Safety of Medicines and Health Products (**ANSM**)

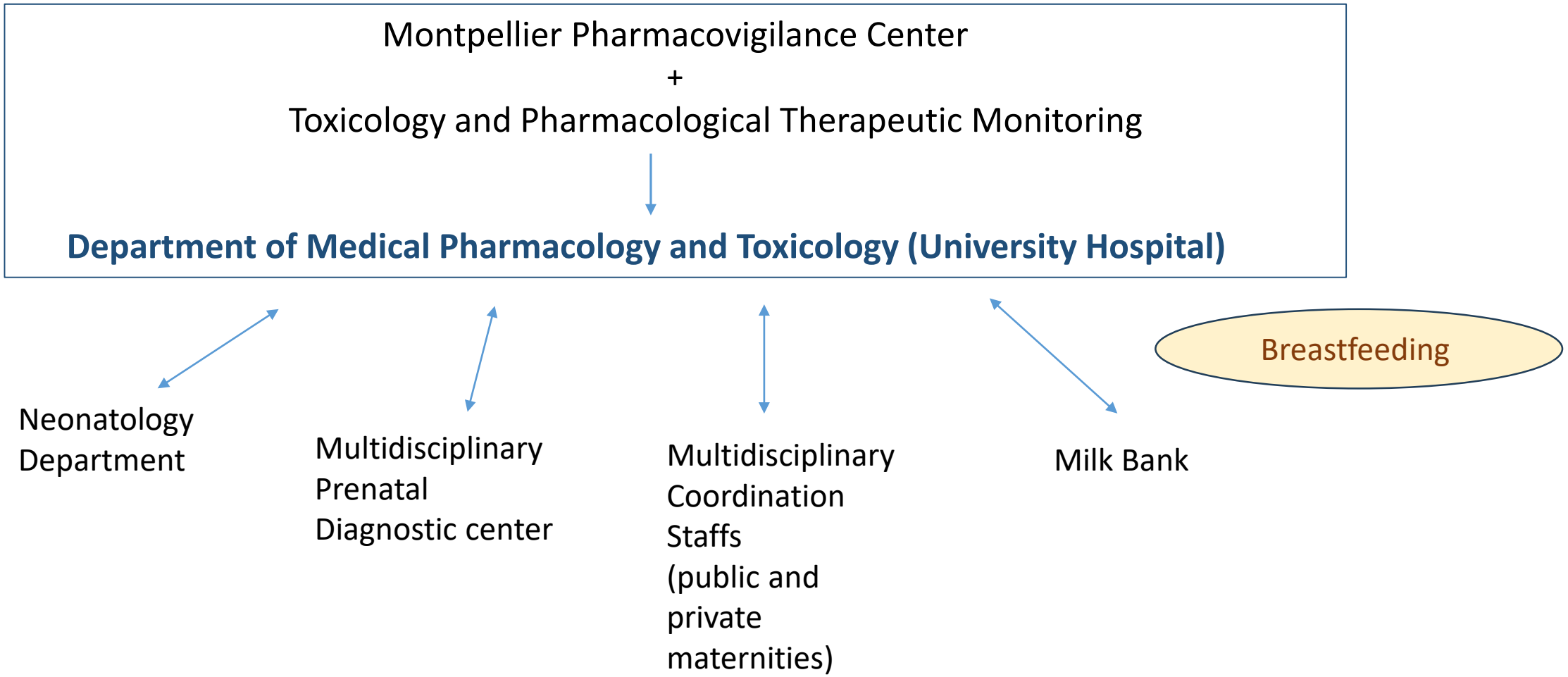
↑ ↓

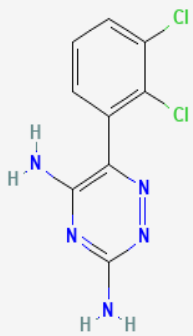
Regional level
Pharmacovigilance Centers (CRPV)

30 centers distributed throughout the territory
in order to promote exchanges with health professionals

Analyze reports of adverse effects related to drug and entry in the national Pharmacovigilance Database
Help health professional with the diagnosis and management of a pathology likely to be due to a drug
Drug risk evaluation, particularly in special populations, as pregnant and breastfeeding woman, neonate
Answer any drug-related questions

For exemple : CRPV Montpellier, around 500 requests/year for pregnancy/breastfeeding and medications





Lamotrigine: first-line antiepileptic treatment for epilepsy/bipolar disorder during pregnancy

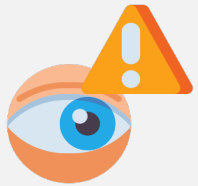
→ extensive data
→ no signal for an increased risk of malformations or neurodevelopmental disorders
→ Rather few cases of poor neonatal adapation

↳ Increase treated women

↳ Tendency to extrapolation pregnancy data to breastfeeding and be reassured

During pregnancy: extensive clearance of lamotrigine

→ Increasd posology in pregnant women
→ supervision and regular dosages are still insufficient
→ no systematic dose adjustment in post partum



Lamotrigine - essential pharmacokinetics

T ½ adult: 33 h (14-59/103)
Plasmatic pic: 2-3 h
T max milk: 3-4h
Oral bioavailability : 98% - Minimal first-pass metabolism effects
Protein binding : 55%
Metabolism : mainly glucuronidation, with inactive metabolite
Renal elimination for drug and metabolites : 94%

Mild milk/plasma ratio : 0,562
Relative Infant Dose : 9,2-18,27%

Premature/new born

Renal and hepatic immaturity, very low activity CYP3A4
Poor neonatal metabolism (glucuronidation)

↳ Elevated free lamotrigine concentrations
↳ Increased plasma half lives

Base de données publique des Médicaments, 2023, Hale TW, medications and mother's milk, 2021 – Newport DJ, Pediatrics, 2008

Main adverse serious effects in treated patients

- Cutaneous reactions (DRESS)
- Hematologic damage (neutropenia…)
- Hepatotoxicity
- Neurologic disorders

Adverse effects reported in breastfed child (publications)

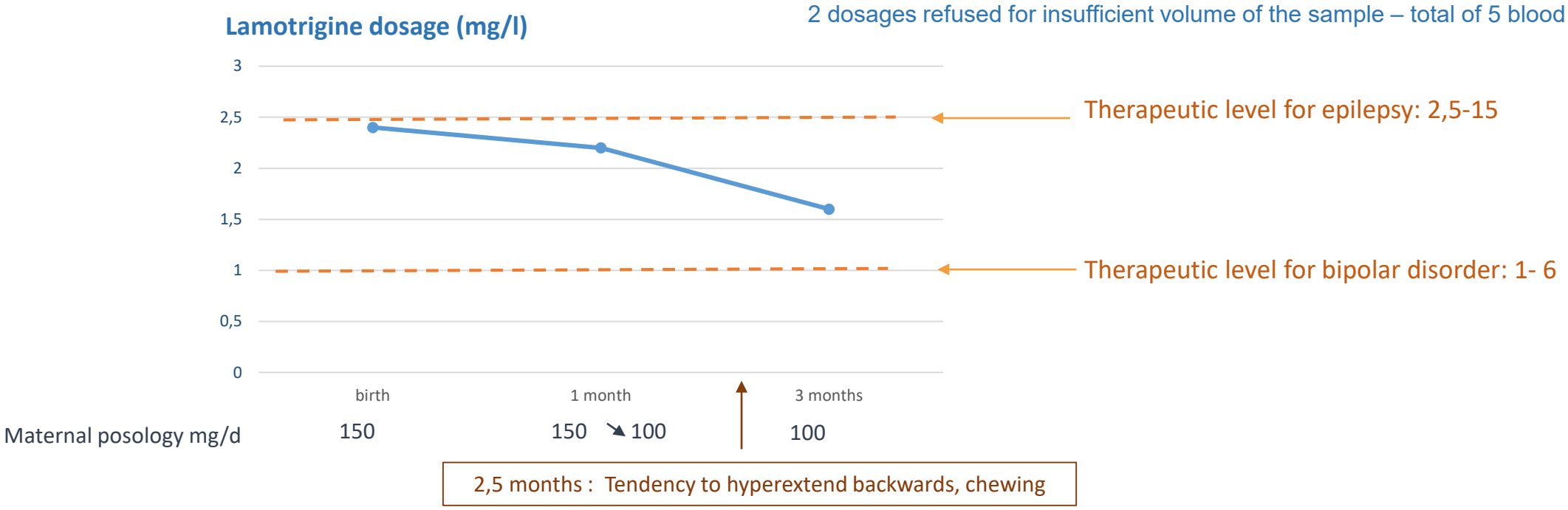
- anemia, neutropenia (mother 150 mg/j)
- severe apnea (mother 850 mf/j)
- elevated liver enzymes lamotrigine serum levels : 2,3-2,6µg/ml)
- elevated liver enzymes (mother 200 mg/j, premature)
- withdrawal after 1-2 weeks breastfeeding stopped (mother 200 mg/j
- rash (2 cases, mothers : 200-250 mg/j)
- sedation, hypotonia, weigh loss (6 infants)

Bedussi F, J Ped Child Health, 2018 - Nordmo E, Ann Pharmacother, 2009 – Padberg S, Reprod Toxicol, 2008 – Precourt A, Breastfeed Med, 2011 – Popescu L, Epilepsia, 2005 – Wakil L, Psychopharmacol Bull, 2009 – Soussan C, Eur J Clin Pharmacol, 2014

French Pharmacovigilance Database : 15 cases of adverse drug reactions with breastfeeding on lamotrigine

	Hepatic disorder	Hematologic disorder	Neurologic Disorder	General disorder	Skin disorder	Other	Recover after stopping breastfeeding	Age	Lamotrigine mother's dosage (100 mg/d)	Lamotrigine Infant plasma level dosage mg/l
Case 1	Hepatic cytolysis	Neutropenia					×	1 month	100	
Case 2	Hepatic cytolysis			weigh loss		Lamotrigine overdose	×	Day 13	150	19,6
Case 3			drowsiness	weigh loss			×	Day 21	50	0,9
Case 4			drowsiness	weigh loss		suckling difficulties	×	Day 14	400	
case 5		Thrombocytosis					×	2 months	150	0,45
case 6	Hepatic cytolysis	Neutropenia Thrombopenia					×	2 months	150	
Case 7	ElevetaedTGO TGP						×	Day 22	100	
Case 8	Prolonged neonatal icterus						×	Day 4	150	1,26
Case 9						Rectorragia Enterolitis	Rectorragia	Day 17	300	
Case 10	ElevetaedT GO TGP						×	1 month	250	2,2
Case 11			drowsiness	weigh loss			×	Day 13	400	1,7
Case 12	Elevetaed TGO TGP						×	Day 14	-	<0,30
Case 13			drowsiness Hyptotonia tremor				×	Day 7	150	1,8
Case 14	Elevetaed TGO TGP GGT						Unknowned	Day 22	350	2,6
Case 15					lichen striatus		Unknowned	5 months	100	

Child 1



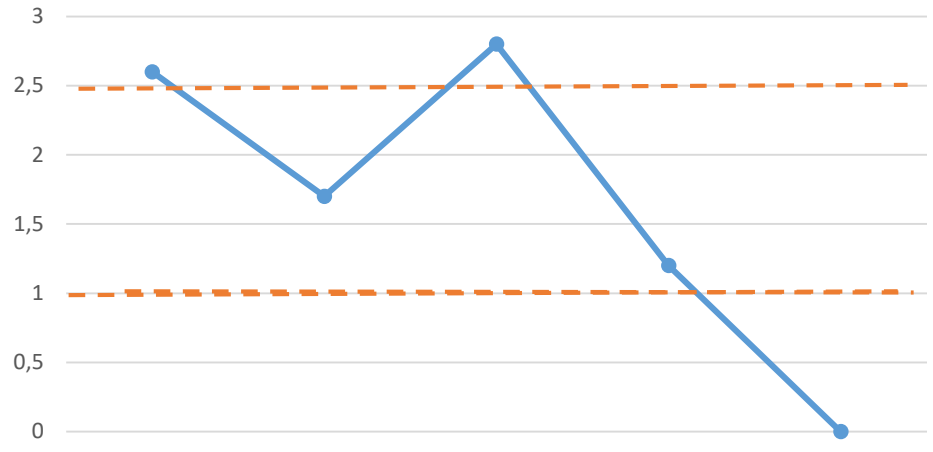
- **Epileptic mother** : lamotrigine 125 mg/d, increased to 150 mg/j during pregnancy
- Intrauterine growth retardation (small for gestational age) until 2nd trimester, (unknowned etiology)
- End pregnancy : thrombopenia (around 120 G/L)
- Induced labor at 38 GW, birth weigh 2430 g

- **Child** : birth, good health. Blood count, liver enzymes normal (control at J30, J90)

Child 2

Lamotrigine dosage (mg/l)

1 dosage refused for insufficient volume of the sample - total of 6 blood samples



Therapeutic level for epilepsy: 2,5-15

Therapeutic level for bipolar disorder: 1- 6

Maternal posology mg/d	J3	J23	2 months	3 months	4 months
	400	400	400	400?	400?

Some spontaneous Moro reflexes
Trend to hypertonia

Gradual weaning onset

3 bottles/d

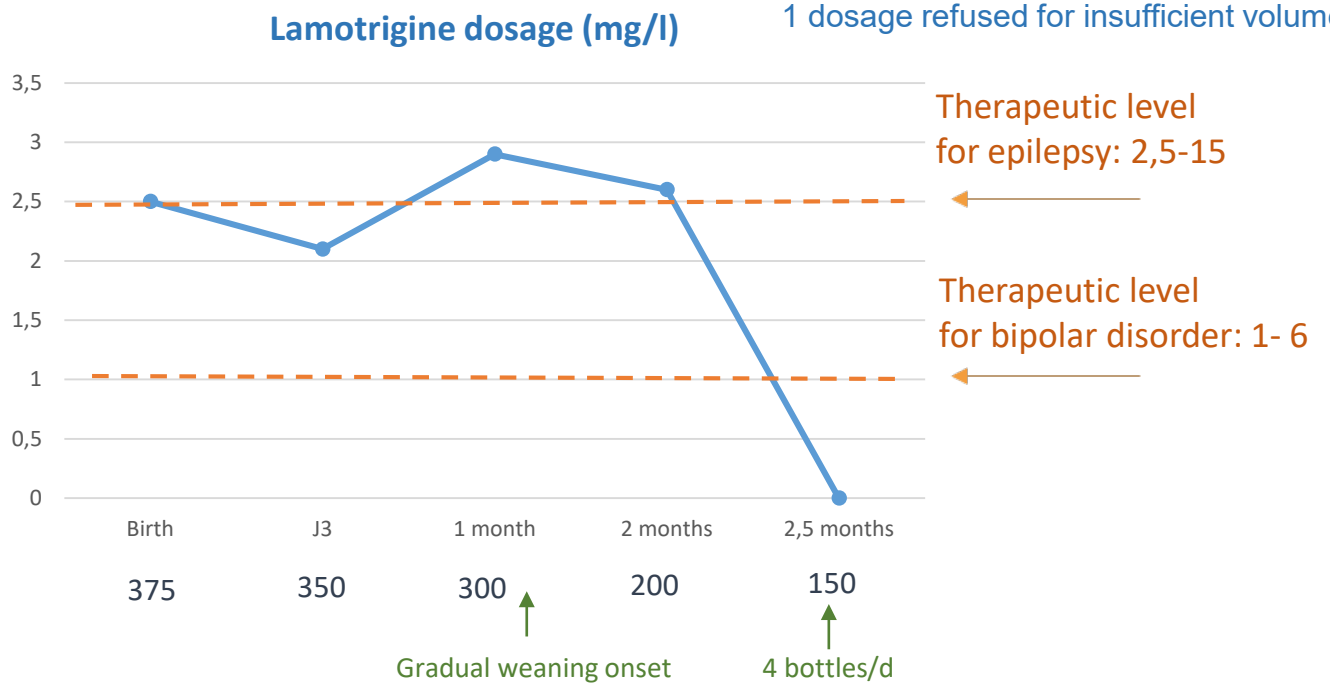
No Moro reflexes

4 bottles/d
2 breast feedings/d

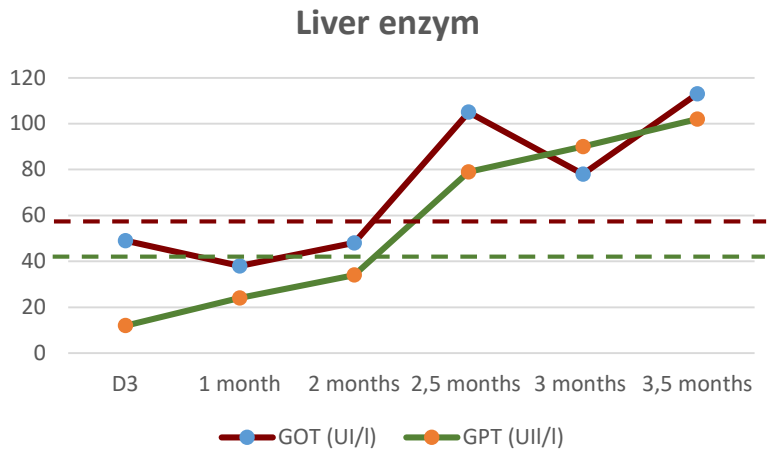
- **Epileptic mother :** lamotrigine 400 mg/d
- Delivery at 38 GW, birth weigh 3145 g
- Brother with anxiety and speech disorders

- **Child** Birth: unremarkable clinical examination
- liver enzymes normal (control at J21, J30, 2 months, 3,5 months)
- 8 months : very good evolution

Child 3

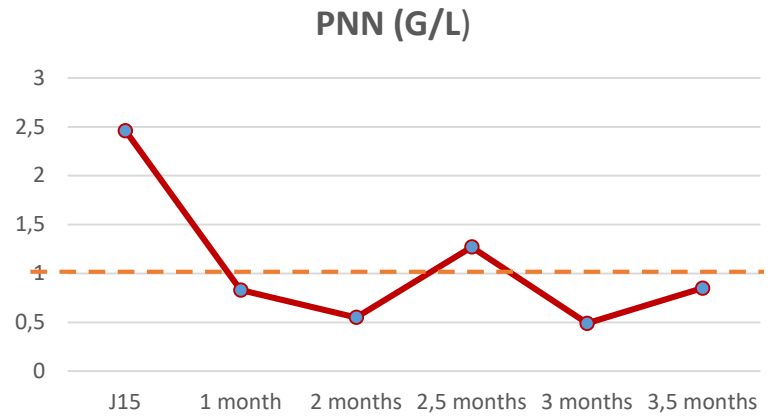


1 dosage refused for insufficient volume of the sample - total of 7 blood samples



No etiology found

- **Epileptic mother** : lamotrigine 200 mg/d, increased to 375 mg/j during pregnancy because of seizures
- Delivery at 41 GW, birth weigh 3460 g



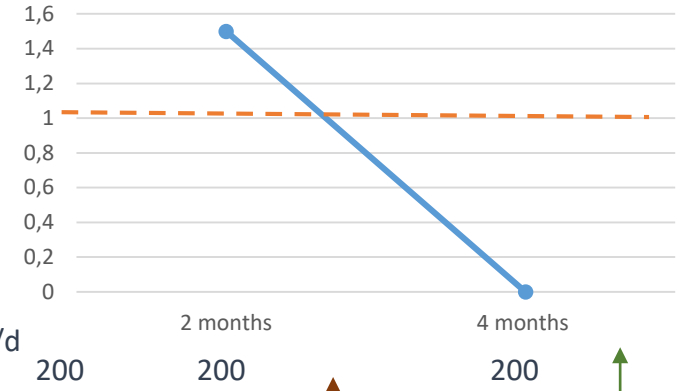
No etiology found

- **Child:** J3, bilateral adduct thumb.
- Open hands at 3 months, remained one incomplete adduct thumb

Child 4

Lamotrigine (mg/l)

2 dosages refused for insufficient volume of the sample - total of 5 blood samples



Therapeutic level
for bipolar disorder: 1- 6

Maternal posology mg/d

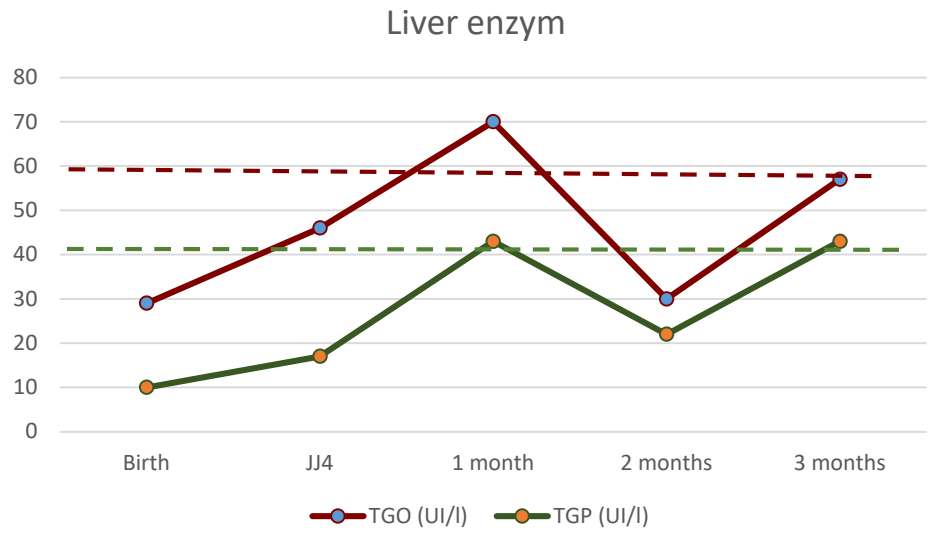
200 200 200

Birth: Jaundice
Lamotrigine <1 mg/l
Mild thrombopenia:
126 G/l, normalised J3

Change in behavior according to mother (fewer feeding, more sleep during the day). Candelstick position, backward hyperextension (physiotherapy).

Stop breastfeeding

Starting introduction of bottle feeding



- **Mother**: ADHD, bipolar disorder. Lamotrigine, 200 mg/d
- Pregnancy by in vitro fertilization
- Induced labor for membrane rupture : 37 SA, birth weigh 2590 g

- **Child:** Apnea detector at home
  - some episodes at 4 sem, and around 7 months. Absence of central apnea
- 9 mois (02/06/22) : marked improvement in hypertension
- 14 mois (21/11/22) : very good evolution

Child 5

- **Mother:** anxious and eating disorder
- Lamotrigine, 50 mg/d, oxazepam, hydroxyzin (unknowned dosage)
- Induced labor: 42 Sa, birth weigh 3470g

- **Child**: Birth, central apnea with global immaturity, cafeine treatment (1 month) and scope
- Mixed feeding until birth - Breastfeeding stopped after the first 3 weeks.

- Lamotrigine levels : 1 result only, J19 <1 mg/l

  (Dosage at birth and J8 not realised, insufficient sample quantity – total of 3 dosages)

- Blood count normal - Liver enzymes : normal (control J 21 Ok)
- J 21: plagiocephaly (torticollis)

Main Data on these 5 cases

Our results confirm those of the literature (*limitations : lamotrigine mother's levels unknowned*)

Average of **5,2 samplings** during their first six months of life (just for lamotrigine dosage)

Necessary to have at least 300 µl of plasma, i.e. approximately **1 ml of whole blood**
(for each child, almost 1 sample refused because of insufficient quantity)

Plasma level value corresponding to a **therapeutic level at least once** for all infants
(except 1, maternal posology 50 mg/d)

→ What do we know about long-term exposure to lamotrigine in a child who does not need it?

Plasma levels decreased in each case with gradual breastfeeding weaning and/or maternal dose reduction

During breastfeeding: Neurologic transient signs in 2 children
Elevated liver enzymes in 2 associated with neutropenia in 1

→ Is there a link?

What to in practice?

Complete and enlightened information must be given during pregnancy

- Few adverse effects reported in breastfed infant but these effects could be serious
- Extensive transfer to the child, with achievement of therapeutic levels
- Need for close monitoring of the child, clinical and blood samples

Discussion for each patient

- maternal posology
- epilepsy or psychiatric status
- co-medications
- baby's age and condition

Do the **benefits of breastfeeding** outweigh the **infant's exposure** to anti-epilectic therapy and the potential **consequences for the mother** (maternal sleep deprivation, risk of seizures, maternal dose reduction because of fear for the infant)?

Dilemna : is it worth it?