Workshop GSASA – Clinical Pharmacy II
GSASA congress 2022

# MARCOUMAR® ON THE WELSCH SIDE OF THE RÖSTIGRABEN

Dre Christel Bruggmann, pharmacienne clinicienne

Hôpitaux Universitaires Genève

# COURSE OF THE WORKSHOP

- Clinical case presentation (≈ 10-15 minutes)
- Group analysis (30 minutes)
- Discussion (30 minutes)

# MR G.D., 62 YEARS OLD

- Admission on the 2nd October in the University Hospital of Geneva, for **confusion** and **respiratory insufficiency** in the internal medicine department

- Transfered from Malaga, where he was in holidays, and was hospitalized in end of september for **falls in unclear circumstances**

- Diagnosed with a **pneumonia,** treated with amoxicilline, and an **acute confusional state**

- Transfer to Geneva because of **persistant confusional state**

# PHYSICAL EXAMINATION AND BIOLOGICAL FINDINGS AT ADMISSION

- **General**: somnolent, psychomotor slowing
- **Cardio-vascular**: unremarkable, lower limb edema
- **Respiratory**: eupneic with 3L $O_2$
- **Digestive**: moderate ascites (four quadrants)
- **Neurologic**: Glasgow 14, flapping tremor
- **Urologic**: unremarkable
- **Cutaneous**: unremarkable

- **Biological findings**: Normochromic normocytic anemia, thrombopenia 110 G/l, hepatic perturbation (ASAT/ALAT 4-5N; yGT 295, PAL 219, total bilirubine 33), no electrolites abnormalities, folates 9.8 nmol/L

# MEDICAL HISTORY

- Alcohol use disorder
- Mitral valve replacement with mechanical valve (2001)
- Arterial hypertension
- Dyslipidemia
- Asthma
- Chronic pancreatitis

- **Usual medical treatment :**
  - Phenprocoumone (Marcoumar®) – 3mg in the evening
  - Lisinopril - 10mg in the morning

# DIAGNOSIS AND MANAGEMENT AT THE HOSPITAL

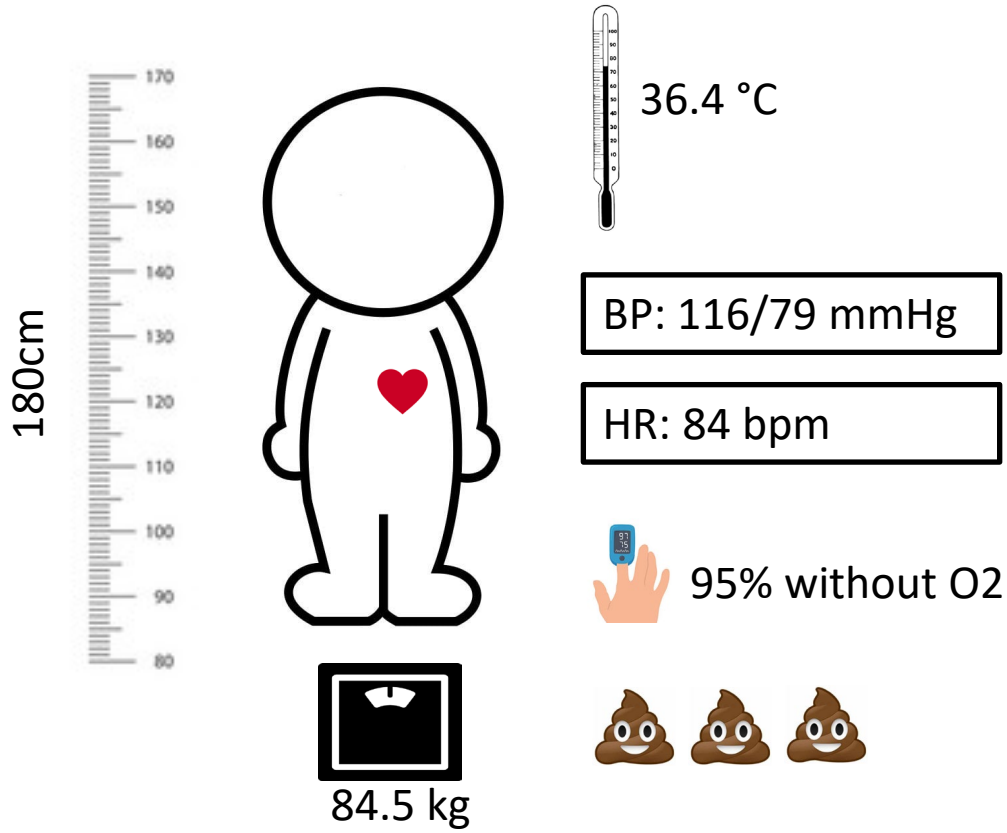
- Alcohol associated **cirrhosis CHILD-PUGH C11** with :
  - Grade 2 **hepatic encephalopathy**
  - Suspicion of **Gayet-Wernicke encephalopathy**
  - Grade 2 **oesophageal varices**
  - **Spontaneous bacterial peritonitis**
  - **Ascitis**

- **Alcohol-associated fatty liver disease (**Maddrey score 40), confirmed by an hepatic biopsy

- **ESBL colonization**

# VITAL PARAMETERS

**Day of medical round (08/10/22) → 6 days after admission in Geneva**



# LAB VALUES - CHEMISTRY

| Dosage | Unité | Seuils | 08.10.2022 06:00 JUL033-US 08 392 sgv | 08.10.2022 06:00 JUL033-US 08 393 sgv | 07.10.2022 06:52 JUL022-US 07 724 sgv | 06.10.2022 06:00 JUL022-US 06 614 sgv |
|---|---|---|---|---|---|---|
| céruloplasmine | g/l | 0.17 - 0.46 | | | | |
| haptoglobine | mg/l | 412 - 1'693 | | | | |
| parathormone | pmol/l | 1.10 - 6.80 | 7.63 | | | |
| 25-hydroxy vitamine D (D2+D3) | nmol/l | > 75 | 11 | | | |
| glucose | mmol/l | 4.1 - 6.0 | | 5.9 | 5.3 | |
| protéine C-réactive | mg/l | 0.00 - 10.00 | | 38.01 | | 66.52 |
| sodium | mmol/l | 136 - 144 | | 139 | 135 | 135 |
| potassium | mmol/l | 3.6 - 4.6 | | 4.1 | 3.7 | 3.5 |
| osmolalité calculée | mOsm/kg | | | 290 | 281 | |
| magnésium total | mmol/l | 0.59 - 0.83 | | 0.64 | | 0.60 |
| calcium total | mmol/l | 2.20 - 2.52 | | 2.37 | 2.22 | 2.25 |
| calcium corrigé | mmol/l | | | 2.59 | 2.56 | 2.57 |
| phosphates | mmol/l | 0.80 - 1.45 | | 0.89 | 0.79 | 0.85 |
| urée | mmol/l | 3.2 - 7.5 | | 7.2 | 6.9 | 7.5 |
| créatinine | µmol/l | 62 - 106 | | 56 | 68 | 93 |
| eGFR (CDK-EPI 2021) | ml/min/1.7... | > 60 | | 107 | 101 | 80 |
| protéines | g/l | 61 - 79 | | 61 | | |
| albumine | g/l | 35 - 48 | | 29 | 23 | 24 |
| lactate deshydrogénase | U/l | 87 - 210 | | | | 141 |
| ASAT | U/l | 14 - 50 | | 131 | 173 | 158 |
| ALAT | U/l | 12 - 50 | | 60 | 77 | 77 |
| phosphatase alcaline | U/l | 25 - 102 | | 156 | 212 | 192 |
| gamma glutamyltranspept. | U/l | 9 - 40 | | 186 | 254 | 245 |
| bilirubine totale | µmol/l | 7 - 25 | | 35 | 44 | 41 |
| bilirubine conjuguée | µmol/l | 0.5 - 9.5 | | 22.5 | 29.9 | 28.4 |

# LAB VALUES - HEMATOLOGY

| Dosage | Unité | Seuils | 08.10.2022 06:00 JUL033-US 08 216 sgv | 07.10.2022 06:52 JUL022-US 07 416 sgv | 06.10.2022 06:00 JUL022-US 06 366 sgv | 05.10.2022 06:34 JUL022-US 05 453 sgv |
|---|---|---|---|---|---|---|
| érythrocytes | T/l | 4.40 - 6.00 | 2.71 | 3.11 | 3.18 | 3.36 |
| hémoglobine | g/l | 140 - 180 | 93 | 103 | 105 | 114 |
| hématocrite | % | 40.0 - 52.0 | 26.5 | 30.1 | 29.9 | 32.6 |
| MCV | fl | 82.0 - 98.0 | 97.8 | 96.8 | 94.0 | 97.0 |
| MCH | pg | 26.0 - 34.0 | 34.3 | 33.1 | 33.0 | 33.9 |
| MCHC | g/l | 320 - 360 | 351 | 342 | 351 | 350 |
| **Réticulocytes** | | | | | | |
| réticulocytes | o/oo Ery | 5.0 - 15.0 | | | 26.5 | |
| réticulocytes-nb.abs | G/l | 20.00 - 120.00 | | | 84.27 | |
| HFR | % | 0.0 - 1.5 | | | 9.0 [A] | |
| Ret-He | pg | 28.0 - 35.0 | | | 38.1 [A] | |
| leucocytes | G/l | 4.0 - 11.0 | 5.3 | 9.2 | 8.3 | 9.0 |
| **Répartition leucocytaire** | | | | | | |
| neutrophiles | % | 33.0 - 80.0 | | | | |
| neutrophiles segmentés | % | 33.0 - 75.0 | 82.0 | | 77.0 | 73.0 |
| neutrophiles non segmnt | % | 0.0 - 5.0 | 5.0 | | 2.0 | 13.0 |
| éosinophiles | % | 0.0 - 5.0 | 0.0 | | 3.0 | 0.0 |
| basophiles | % | 0.0 - 2.0 | 0.0 | | 0.0 | 0.0 |
| monocytes | % | 0.0 - 9.0 | 3.0 | | 9.0 | 10.0 |
| lymphocytes | % | 15.0 - 60.0 | 9.0 | | 8.0 | 4.0 |
| myélocytes | % | 0.0 - 0.0 | 1.0 | | 1.0 | |
| cellules réparties | | | 100 | | 100 | 200 |
| neutrophiles-nb abs | G/l | 1.50 - 8.00 | | | | |
| neutro segmentes nb.abs | G/l | 1.50 - 7.50 | 4.35 | | 6.39 | 6.57 |
| neutro non seg.-nb.abs | G/l | 0.00 - 0.50 | 0.27 | | 0.17 | 1.17 [B] |
| éosinophiles-nb.abs | G/l | 0.00 - 0.40 | 0.00 | | 0.25 | 0.00 |
| basophiles-nb.abs | G/l | 0.00 - 0.20 | 0.00 | | 0.00 | 0.00 |
| monocytes-nb.abs | G/l | 0.00 - 0.80 | 0.16 | | 0.75 | 0.90 |
| lymphocytes-nb.abs | G/l | 1.00 - 4.50 | 0.48 | | 0.66 | 0.36 |
| **Thrombocytes** | | | | | | |
| thrombocytes | G/l | 150 - 350 | 68 | 74 [D] | 78 | 83 |
| MPV | fl | 8.0 - 12.0 | 10.7 [A] | 10.1 [A] | 10.2 [A] | 9.9 [A] |

Hôpitaux Universitaires Genève

# LAB VALUES - INR

| Date | INR | Phenprocoumone (mg) | Date | INR | Phenprocoumone (mg) |
|---|---|---|---|---|---|
| 20/09 | 8.7 | 0 | 30/09 | 3.0 | 3.25 |
| 21/09 | 4.3 | 0 | 01/10 | 3.3 | 3.25 |
| 22/09 | 1.6 | 3.75 | 02/10 | - | 3.75 |
| 23/09 | 1.4 | 3.75 | 03/10 | - | 3.25 |
| 24/09 | 1.5 | 2.75 | 04/10 | 3.6 | 3.75 |
| 25/09 | 2.2 | 3.75 | 05/10 | - | 3.25 |
| 26/09 | - | 2.75 | 06/10 | - | 3.75 |
| 27/09 | 2.1 | 2.75 | 07/10 | 5.6 | 3.25 |
| 28/09 | - | 3.75 | 08/10 | 6.1 | Day of medical round |
| 29/09 | 2.8 | 3.25 | … | … | … |

Vitamine K 10mg

Usual schema dosing with 2,75mg – 3,75mg any other day

Schema modification with 3.75mg – 3.25mg any other day

Hôpitaux Universitaires Genève

# MEDICATION THE DAY OF MEDICAL ROUND

**October 8th prescriptions**:

- Imipenem/cilastatin IV – 500mg 1x/6h
- Folic acid – 5mg q.d.
- Lactilol sir – 30mL t.i.d.
- Magnesium – 12mmol q.d.
- Potassium chloride – 10mmol q.i.d
- Prednisone – 40mg q.d.
- Sodium phosphate – 500mg q.d.
- Spironolactone – 50mg q.d
- Torasemide – 10mg q.d.
- Propranolol - 20mg b.i.d
- Vitamine B1 – 100mg q.d.
- Esoméprazole – 40mg q.d.
- Phenprocoumone – dose to define
- Paracetamol - 500mg q.i.d. if necessary
- Oxazépam 15mg q.i.d if necessary (CIWA > 8)

# QUESTIONS ABOUT THE CASE

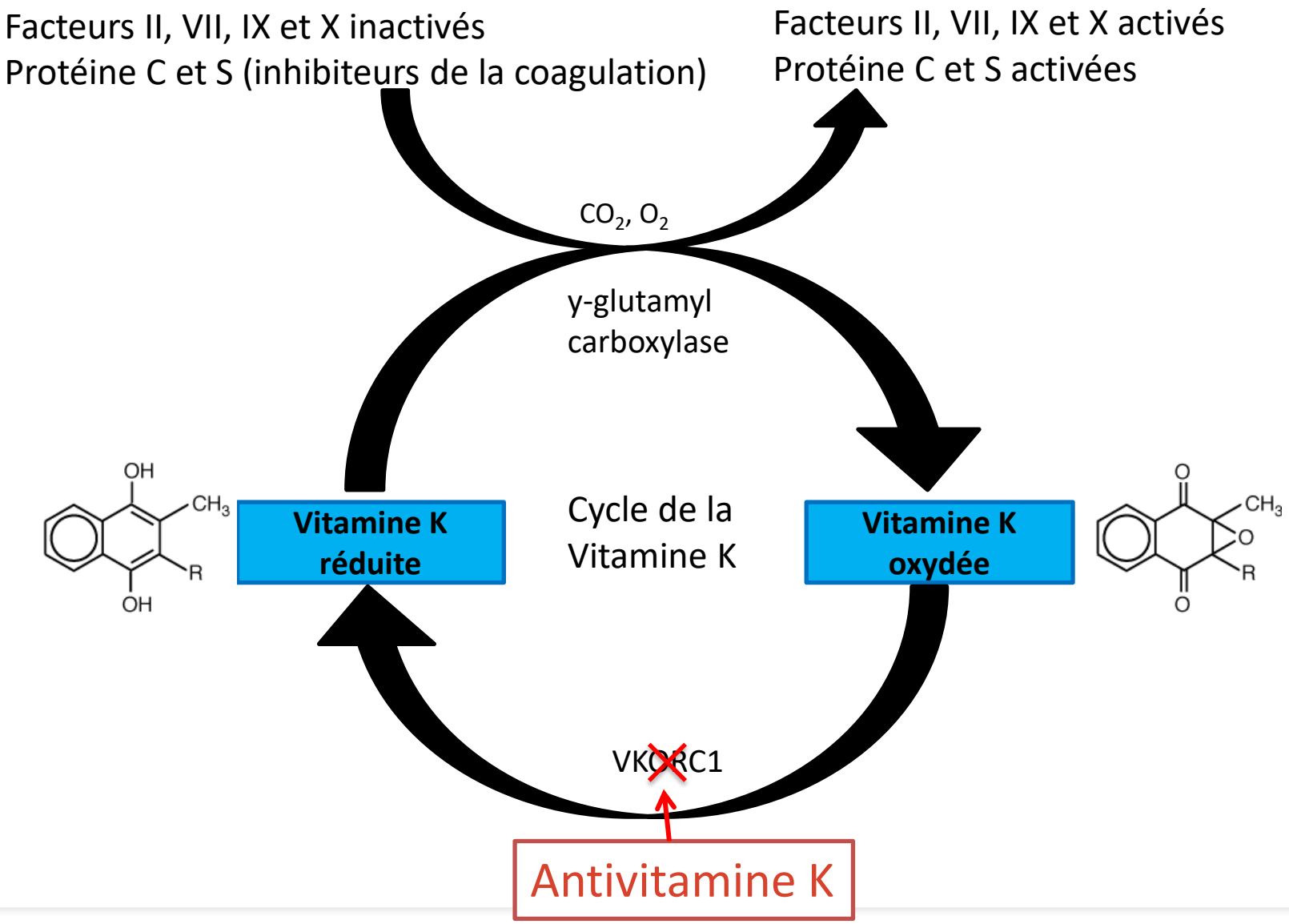
1) What would you recommand for **supratherapeutic INR management**?

2) What **dose of phenprocoumone** would you recommand for the next days?

3) During the medical round, nurses complains about agitation of the patient during the night with insomnia. What would you recommand for him?

4) Is there any **other medications** you would **stop/start** in this case?

# VKA CYCLE QUICK REMINDER




Adapted from Brunton LL, Chabner BA, Knollmann BC : Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition

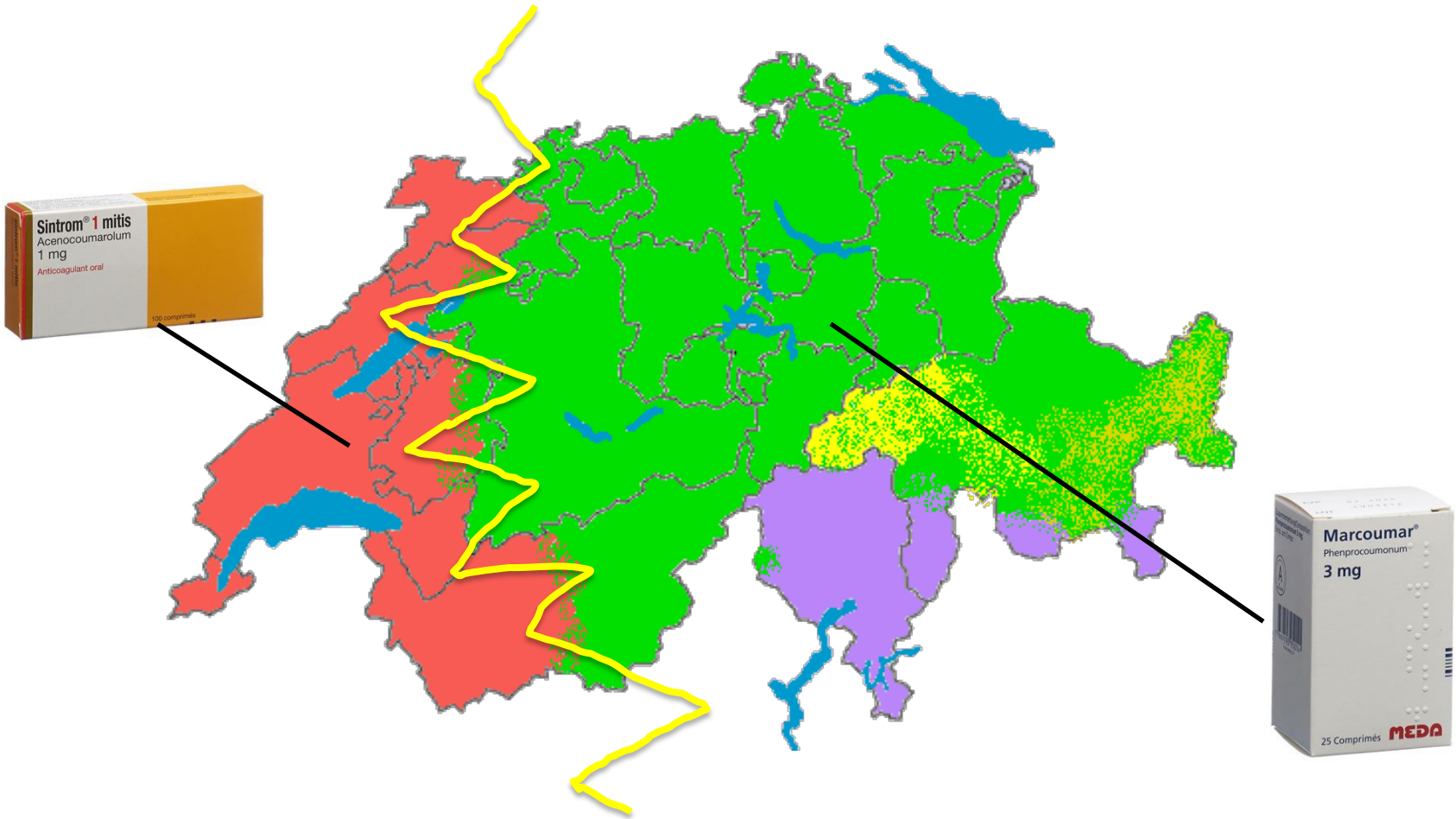
# VKA - MOLECULES

| | $T_{1/2}$ |
|---|---|
| Acenocoumarol (Sintrom®) | 8-11 h |
| Phenprocoumone (Marcoumar®) | 160 h (= 6.6 days) |
| Warfarine (not in CH) | 36-42 h |
| Fluindione (Previscan®) (FR) | 31 h |

For each $t_{1/2}$, ↓ 50% de anticoagulant effect→ 4 x $t_{1/2}$ for 12.5% residual anticoagulant effect

Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson
Compendium Suisse des médicaments

# RÖSTIGRABEN




Boris
JOHNSON

# SUPRATHERAPEUTIC INR MANAGEMENT

| INR | Bleeding | Recommandation |
|---|---|---|
| -> 4.5 | No | AVK dosing reduction |
| 4.5-10 | No | Resume AVK and administer 0.5-1mg Vitamine K per os |
| >10 | No | STOP AVK and administrer 2.5-5mg vit K (per os) → effect on INR in 24-48h<br>Daily INR monitoring<br>Restart AVK with reduced dosing when INR is in the range |

Our proposition for Mr G.D. : - STOP Marcoumar® + 1mg oral vitamine K
- Daily INR monitoring

Hôpitaux Universitaires Genève

1. UpToDate. **Management of warfarin-associated bleeding or supratherapeutic INR**. Accessed in 10/2022

# PHENPROCOUMONE SCHEME

| Date | INR | Phenprocoumone (mg) | Date | INR | Phenprocoumone (mg) |
|---|---|---|---|---|---|
| 20/09 | 8.7 | 0 Vitamine K 10mg | 30/09 | 3.0 | 3.25 |
| 21/09 | 4.3 | 0 | 01/10 | 3.3 | 3.25 |
| 22/09 | 1.6 | 3.75 | 02/10 | - | 3.75 |
| 23/09 | 1.4 | 3.75 | 03/10 | - | 3.25 |
| 24/09 | 1.5 | 2.75 | 04/10 | 3.6 | 3.75 |
| 25/09 | 2.2 | 3.75 | 05/10 | - | 3.25 |
| 26/09 | - | 2.75 | 06/10 | - | 3.75 |
| 27/09 | 2.1 | 2.75 | 07/10 | 5.6 | 3.25 |
| 28/09 | - | 3.75 | 08/10 | 6.1 | Day of medical round |
| 29/09 | 2.8 | 3.25 | … | … | … |

Initial INR reduction due to administration of vitamine K, but INR elevation due to **end of vitamine K effect** and not to the raise of phenprocoumone dose

Hôpitaux Universitaires Genève

# PHENPROCOUMONE SCHEME

| Date | INR | Phenprocoumone (mg) | Date | INR | Phenprocoumone (mg) |
|---|---|---|---|---|---|
| 20/09 | 8.7 | 0 Vitamine K 10mg | 30/09 | 3.0 | 3.25 |
| 21/09 | 4.3 | 0 | 01/10 | 3.3 | 3.25 |
| 22/09 | 1.6 | 3.75 | 02/10 | - | 3.75 |
| 23/09 | 1.4 | 3.75 | 03/10 | - | 3.25 |
| 24/09 | 1.5 | 2.75 | 04/10 | 3.6 | 3.75 |
| 25/09 | 2.2 | 3.75 | 05/10 | - | 3.25 |
| 26/09 | - | 2.75 | 06/10 | - | 3.75 |
| 27/09 | 2.1 | 2.75 | 07/10 | 5.6 | 3.25 |
| 28/09 | - | 3.75 | 08/10 | 6.1 | Day of medical round |
| 29/09 | 2.8 | 3.25 | … | … | … |

Accumulation of phenprocoumone

# PHENPROCOUMONE SCHEME

## Our proposition for Mr G.D. :

1) Administer **low dosing Vitamine K (0.5-1mg)**
2) Resume phenprocoumone **for minimum 3-4 days** → we would expect a reduction of 50% anticoagulation effect after 6-7 days without phenprocoumone → We would expect an **INR around 4**
3) Daily INR monitoring → if INR raises again (due to end of vitamine K effect) → readminister Vitamine K low dosing
4) Restart phenprocoumone with **reduced dosing** (2.25-3.0mg) once INR is slightly above therapeutic range
5) Monitore INR at day 7 and adapt dosing

# HEPATIC ENCEPHALOPATHY - PATHOGENESIS

Many hypothesis and multifactorial, but the three major hypothesis are:

- **Hyperammoniemia**
  - Production from protein metabolism in the GI tract by bacteria → polypeptides + amino acids + ammonia
  - Ammonia metabolized in the liver in urea → accumulation in cirrhosis
  - In the CNS, ammonia combine with α-ketoglutarate to form glutamine in astrocytes → osmotic imbalance, cell swelling and brain edema
- **Amino-acid imbalance**
  - **↓ branched chain amino acids** (valine, leucine, isoleucine) and **↑ aromatic amino acids** (phenylalanine, tyroisine, methionine)
  - Highly permeability of aromatic amino acids in the BBB → phenylalanine leads to production of false neurotransmitters replacing ususal neurotranmitter (e.g. dopamine)
- **Enhancement of GABA-ergic neurotransmission**
  - GABA escapes hepatic metabolism due to cirrhosis, cross blood-brain barrier, binds to receptors and causes neurologic abnormalities



https://www.fmcgastro.org/texte-postu/postu-2020-paris/encephalopathie-hepatique/
UpToDate. Hepatic encephalopathy: Pathogeneis. Accessed the 29th october 2022

# HEPATIC ENCEPHALOPATHY - TREATMENT

- **Avoiding precipiting factors:**
  - GI bleeding, infection (PBS), Hypokaliemia, Hypoxia, sedative use, constipation, hypoglycemia
- **Lower blood ammoniemia**:
  - Lactilol, lactulose → 3 stools per day
  - Rifaximine → as an alternative to lactilol, lactulose
  - L-ornitine-L-asparte (LOLA) → controversial efficacy → not approved in CH
  - Oral nutritional therapy
- **Restoring Amino-acid balance**
  - Branched chain amino-acids (BCAAs) → restoration of balance
  - Meta-analysisshowed no benefit with regard to mortality (relative risk [RR] 0.8, 95% CI 0.7-1.1), but **beneficial effect on hepatic encephalopathy** (RR 0.7, 95% CI 0.6-0.9)
  - Not approved in CH
- **Reduction of GABA-ergic neurotransmission**
  - Avoidance of benzodiazepines/barbiturates

Hôpitaux Universitaires Genève

https://www.fmcgastro.org/texte-postu/postu-2020-paris/encephalopathie-hepatique/
UpToDate. Hepatic encephalopathy: Pathogeneis. Accessed the 29th october 2022
Gluud LL and al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2017

# HEPATIC ENCEPHALOPATHY - SEDATIVES

To avoid
- Benzodiazepines
- Opioids
- Antihistamines
- Antipsychotics

→ Risk of oversedation, specially for BZD

Sedatives which could be considered
- Haloperidol → based only on clinical experience and scarce data
- Melatonine → Proof that melatonine rise is delayed by hours. No clinical data about efficacy

Our proposition for Mr G.D. → melatonine 2 hours before bed, and oral haloperidol 0.5mg in case of severe agitation

Hôpitaux Universitaires Genève

UpToDate. Hepatic encephalopathy: Pathogeneis. Accessed the 29th october 2022
Prabhakar S et al. Management of agitation and convulsions in hepatic encephalopathy. Indian J gastroenterol. 2003.

# OTHER DRUG RELATED PROBLEM

## Propranolol and Spontaneous bacterial peritonitis

CLINICAL LIVER

### Nonselective β Blockers Increase Risk for Hepatorenal Syndrome and Death in Patients With Cirrhosis and Spontaneous Bacterial Peritonitis

Mattias Mandorfer,[1,2] Simona Bota,[1,2] Philipp Schwabl,[1,2] Theresa Bucsics,[1,2] Nikolaus Pfisterer,[1,2] Matthias Kruzik,[1,2] Michael Hagmann,[3] Alexander Blacky,[4] Arnulf Ferlitsch,[1,2] Wolfgang Sieghart,[1,2] Michael Trauner,[1,2] Markus Peck-Radosavljevic,[1,2] and Thomas Reiberger[1,2]

*[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [2]Vienna Hepatic Hemodynamic Lab, Vienna, Austria; [3]Section for Medical Statistics, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria; and [4]Clinical Institute of Hospital Hygiene, Vienna General Hospital, Vienna, Austria*

This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this exam, successful learners will be able to identify patients with cirrhosis and ascites that no longer benefit from non-selective β blocker treatment since the development of spontaneous bacterial peritonitis indicates an event when non-selective beta-blockers can compromise the circulatory reserve.

# OTHER DRUG RELATED PROBLEM

**Propranolol and spontaneous bacterial peritonitis**

Retrospective study
607 patients included

**Inclusion criteria** : diagnosis of cihrrosis and ascitis

**Results :**

↗ 58% in mortality risk in patients receiving β-blocker (hazard ratio [HR] 1.58, 95% CI 1.10-2.27)

↗ hepatorenal syndrome (24 versus 11 percent)

↗ length hospital stay (29.6 versus 23.7 days)

Our proposition for Mr G.D. → STOP propranolol

# OTHER DRUG RELATED PROBLEM

**Balance torasemide/spironolactone**

Most successfull balance for ascites = 40mg oral furosemide + 100mg spironolactone

- Better efficacy in asites reduction than furosemide alone
- Best dose combination to maintain normokaliemia

40mg oral furosemide = 10mg torasemide → 10mg torasemide + 100mg spironolactone

Our proposition for Mr. G.D. → increase spironolactone dose to 100mg



Fogel MR. Diuresis in the ascitic patient: a randomized controlled trial of three regimen. J Clin Gastroenterol (1981)
Angeli P et al. Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: results of an open randomised clinical trial. Gut (2010)

# CATAMNESIS

- Mr G.D. was transfered to rehabilitation on the 28th october
- Propranolol was stopped and he benefited from variceal ligation
- Ascites were well controlled with torasemid 10mg/spironolactone 100mg, without need for potassium repletion
- INR was finally controlled after phenprocoumone was stopped for 3 days and restart with lower dosing

Unfortunately, Mr G.D. was readmitted in internal medicine from rehabilitation because of sever hypercalcemia….

But this is another story!

# THANK YOU FOR YOUR ATTENTION

christel.bruggmann@hcuge.ch

Hôpitaux
Universitaires
Genève

# ANNEXES

# SCORES

**Score de Maddrey** = 4,6 x [TP patient (sec) – TP contrôle (sec)] + bilirubine (µmol/l)/17

Exemple: TP 62%, bilirubine 78 µmol/l:
Score de Maddrey = 4,6 x (16 – 12,3) + 78/17 = 17 + 4,6 = 21,6

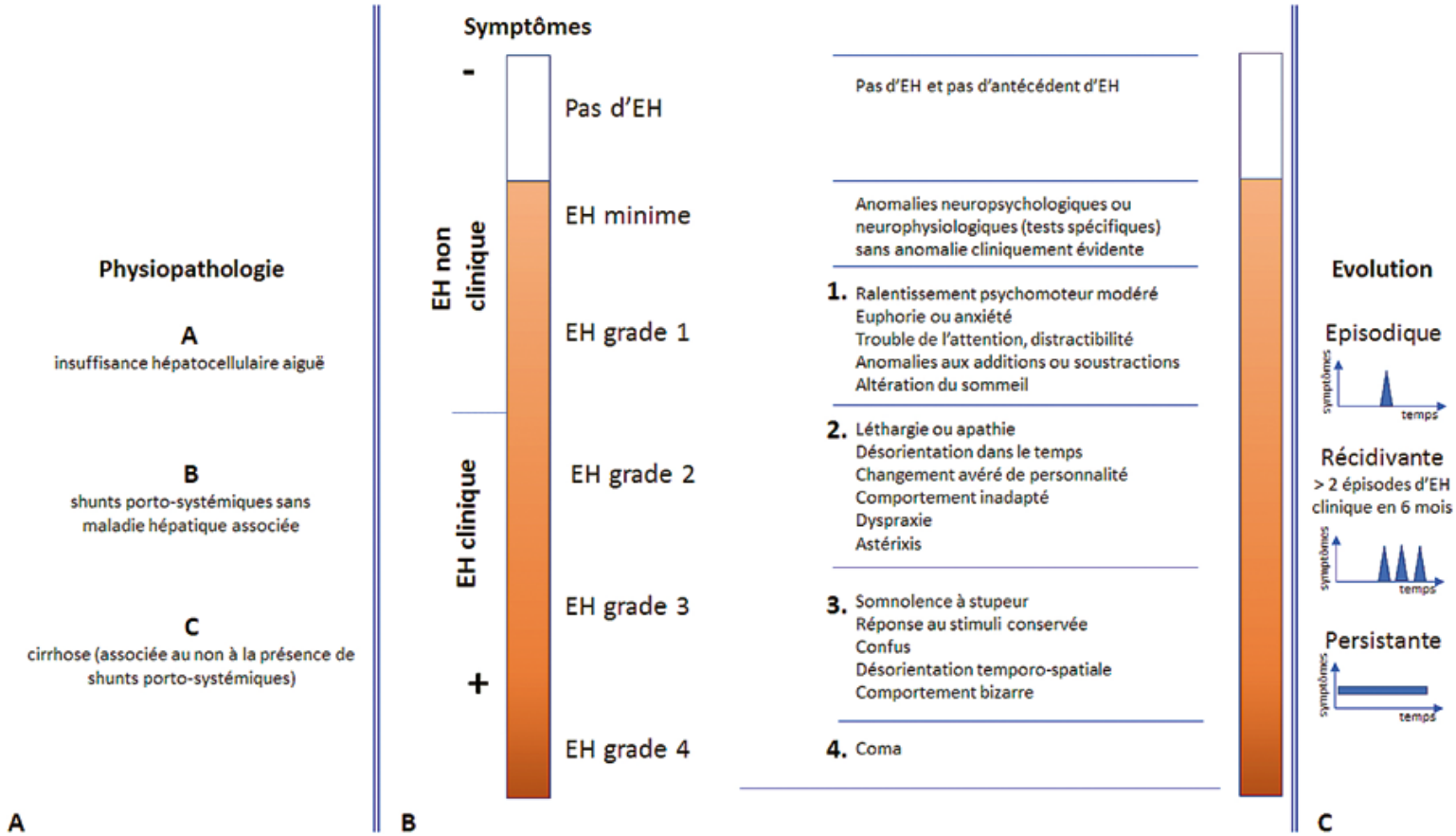
**Tableau 1**
**Score de Child-Pugh**
INR : International normalized ratio ; TP : taux de prothrombine.

| | 1 point | 2 points | 3 points |
|---|---|---|---|
| **Ascite** | Absente | Modérée | Tendue ou réfractaire aux diurétiques |
| **Bilirubine (µmol/l)** | < 35 | 35-50 | > 50 |
| **Albumine (g/l)** | > 35 | 28-35 | < 28 |
| **INR**<br>**TP** | < 1,7<br>> 50% | 1,7-2,2<br>40-50% | > 2,2<br>< 40% |
| **Encéphalopathie** | Absente | Légère à modérée (stade 1-2) | Sévère (stade 3-4) |

Le pronostic de la cirrhose est établi en fonction du score total des points:
**Child-Pugh A** (5-6 points): survie à 1 an de 100%
**Child-Pugh B** (7-9 points): survie à 1 an de 80%
**Child-Pugh C** (10-15 points): survie à 1 an de 45%

$$\text{MELD} = 3{,}8 \times \log_e (\text{bilirubine totale en mg/dl}) + 11{,}2 \times \log_e (\text{INR}) + 9{,}6 \times \log_e (\text{créatinine en mg/dl}) + 6{,}4$$

# HEPATIC ENCEPHALOPATHY - CLASSIFICATION




Hôpitaux Universitaires Genève

https://www.fmcgastro.org/texte-postu/postu-2020-paris/encephalopathie-hepatique/

## Grading system for hepatic encephalopathy

| Grade | Mental status | Asterixis | EEG |
|---|---|---|---|
| I | Euphoria/depression | Yes/no | Usually normal |
| | Mild confusion | | |
| | Slurred speech | | |
| | Disordered sleep | | |
| II | Lethargy | Yes | Abnormal |
| | Moderate confusion | | |
| III | Marked confusion | Yes | Abnormal |
| | Incoherent | | |
| | Sleeping but arousable | | |
| IV | Coma | No | Abnormal |

EEG: electroencephalogram.