MUNI MED

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CZECH RECOVERY PLAN

MINISTRY OF EDUCATION, YOUTH AND SPORTS

Therapy of symptoms of liver failure

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Learning outcomes

- *The student will outline general therapy for the most common symptoms accompanying liver failure.*
- *The student will explain the mechanism of action of the drugs used.*
- *The student will justify the selection of a specific drug for a specific patient.*
- *The student will plan drug dose adjustment, monitoring safety and efficacy of therapy.*

Pharmacotherapy of associated symptoms

Drugs reducing pressure in the portal circulation, splanchnic blood flow

- ***Beta-blockers*** (BB)
  - Non-selective BB (*propranolol* – individually compounded, nadolol), ***carvedilol***
  - Mechanism:

    propranolol (ev. nadolol) – β2 rp. blockade while maintained activity of α1 rp. (inflow reduction) + β1 blockade in higher dosage

    carvedilol – β2 rp. blockade and α1-lytic activity + β1 blockade in higher dosage (higher efficacy comparing to the non-selective)
  - Dose titration according to the tolerance (cardiovascular) or effect/HPVG, AE

    propranolol from 2×20 mg, ev. 1×20 mg

    carvedilol from 2×12,5 mg, ev. 2×6,25 mg
  - Watch out for the impact of changes in pharmacokinetics (FPE, circulation)
  - Efficacy of other BB unclear
  - Used in primary prophylaxis

	bioavai-lability	FPE	protein binding	plasma half-life	renally unchanged	receptor profile
atenolol	40 %	0	10 %	6–7	>90 %	β1
metoprolol	50 %	++	12 %	3–7	5–10 %	β1
bisoprolol	90 %	0	30 %	9–12	50 %	β1
carvedilol	30 %	++	>95 %	6–10	<2 %	β1–β2; α
nebivolol	12–96 %	+++	98 %	10	<0,5 %	β1

Pharmacotherapy of associated symptoms

Drugs reducing pressure in the portal circulation, splanchnic blood flow

- ***Vasopressin*** and its analogues
  - ***Vasopressin***

    Mechanism: V1 rp. stimulation – systemic and splanchnic vasoconstriction, V2 rp. stimulation – water retention

    Adverse effects: splanchnic, cardiac, brain ischemia + negative chronotropic and inotropic effect + water retention (risk if dilutional hypoNa)

  - Vasopressin and nitroglycerine

  - ***Terlipressin*** as a prodrug (= triglycyl-lysin-vasopressin)

    Cleavage of glycyl by endothelial peptidases; prolonged effect with the possibility of bolus administration and minimization of AEs),

    More localized effect, longer $T_{1/2}$ (0.5–1–2 mg q 4–6 h – titration to the effect)

    Adverse effects: abdominal cramps, diarrhea (vs. lactulose?)

Pharmacotherapy of associated symptoms

Drugs reducing pressure in the portal circulation, splanchnic blood flow

- ***Somatostatin*** and its analogues (***octreotid***)
  - Mechanism: inhibits secretion of a number of vasoactive substances in the GIT – localized effect, selective splanchnic vasoconstriction + blockade of postprandial dilation and increase in mesenteric flow
  - Adverse effect: decrease in renal perfusion

Pharmacotherapy of associated symptoms

Drugs of the spontaneous bacterial peritonitis – prevention, therapy

→ Prevention

- ***Co-trimoxazole*** (960 mg/day), ***norfloxacine*** (400 mg/day), ***ceftriaxone*** (1 g/day in patients with cirrhosis and GI bleeding – reduction of mortality, SBP, rebleeding; then co-trimoxazole, ev. norfloxacine in a higher dosage)
- In patients with cirrhosis and GI bleeding, with previous episode of SBP,…
- Concomitant treatment with diuretics

→Therapy

- ***Cefotaxime*** (2 g q 8 hrs), ***ceftriaxone*** (2 g/day), ***ciprofloxacine*** (400 mg q 12 hrs; risk of resistance if quinolones in prophylaxis), ev. carbapenems
- The above rather than a narrower-spectrum ATB; the ATB should cover typical pathogens and have a good penetration into ascites
- Dose adjustment vs. changes in pharmacokinetics
- Be aware of nephrotoxic ATBs

Pharmacotherapy of associated symptoms

Drugs for the therapy of encephalopathy

→ Prevention/elimination of precipitating factors
→ Decrease in ammonemia (symptomatic)

- ***lactulose***
  - Mechanism:

    pH change in the intestine, ammonia ionization, limitation of resorption

    Laxative effect, support of NH_3 utilization by bacteria, change of microbiome
  - Dose titration to the effect (30–45 ml 2–4 times/day; target 2–4 stools/day) or tolerance (number of stools, sweet taste, adverse effects: bloating, diarrhoea, cramps)
  - Typically 1st choice of hyperammonemia therapy

Pharmacotherapy of associated symptoms

Drugs for the therapy of encephalopathy

→ Prevention/elimination of precipitating factors
→ Decrease in ammonemia (symptomatic)

- ***rifaximin***
  - Mechanism: a non-absorbable intestinal ATB, microbiome alteration, barrier properties, decrease in translocation
  - Alone or in combination with lactulose
- ***branched-chain amino acids*** (valine, leucin, isoleucine)
  - Mechanism: change in the ratio of aromatic and branched amino acids
  - For protein intolerant patients vs. protein intake 1.2–1.5 g/kg/day, total 35–40 kcal/kg/day, balanced intake during the day incl. „the 2nd dinner“

+ Prevention of Wernicke‘s encephalopathy - ***thiamine***

Pharmacotherapy of associated symptoms

Drugs for the alcohol withdrawal syndrome, delirium

→ A separate topic

- ***clomethiazole***
  - Indicated for the treatment of restlessness, agitation, and confusion in the elderly, for sleep disorders in elderly, for acute withdrawal states in the treatment of alcohol abusers and for delirium tremens
  - Soft, greyish-beige capsules containing a faint yellow to yellow, clear, oily liquid with a mild, pleasant odour
    - Not suitable for the administration by tube!
    - Risk of drug sorption into and permeation through plastic, risk of plastic softening
  - Therapeutic alternatives: benzodiazepines, propofol may be considered for i.v. administration in some cases

Pharmacotherapy of associated symptoms

Drugs for the coagulopathy

- ***vitamin K***
  - Mechanism: substitution
  - Especially in patients with cholestasis, malnutrition, cirrhosis, pancreatic dysfunction, diarrhoea, and ATB therapy
  - The response may help to assess to degree of synthetic liver (dys)function but does not help in the assessment of the risk of bleeding/thrombosis
  - 10 mg p.o./i.v. several days (limited rate of i.v. inj. – risk of anaphylaxis), in acute conditions better i.v.

Pharmacotherapy of associated symptoms

Drugs for the coagulopathy

- ***Plasma (FFP, fresh frozen plasma), cryoprecipitates***
  - Mechanism: substitution
  - Only in the therapeutic setting (active, limited controlled bleeding), not in the prevention of asymptomatic

- *Prothrombin complex concentrate(PCC), fibrinogen, recombinant activated factor VII*
  - Costly, thrombotic risk, limited evidence

- **Risk drugs**: depending on the status of liver disease/compensation – *antithrombotics* (decision on whether to deploy in the prophylactic/therapeutic indications), *indirect anticoagulants*, *NSAID*

Pharmacotherapy of associated symptoms

Drugs for the therapy of pruritus

- ***H1-receptor antagonists***
  - Keep in mind the sedative effects

- ***Corticosteroids***
- ***Ursodeoxycholic acid (UDCA)***
- ***Rifampicin, phenobarbital***

Take home message

- Depending on the etiology of liver failure, there may be a specific therapy; however, depending on the specific presentation, it is often combined with symptomatic therapy.
- Symptomatic therapy may be aimed at influencing portal pressure and splanchnic blood flow, prevention and treatment of SBP, encephalopathy, delirium, coagulopathy, pruritus or combinations thereof.
- The use of any drugs should take into account changes in their pharmacokinetics and pharmacodynamics in patients with hepatic failure.

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