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Trends in the Design and Conduct of Pharmacokinetic Studies in Patients with Impaired Hepatic Function

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PURPOSE

A pharmacokinetic (PK) study in patients with impaired hepatic function should be conducted in the following situations:

- if hepatic metabolism and/or excretion accounts for a substantial portion (>20 percent of the absorbed drug) of the elimination of a parent drug or active metabolite;
- in the case of a narrow therapeutic range drug, and;
- if metabolism of the drug is unknown.

The design and conduct of these hepatic impairment (HI) studies may have evolved since the latest version of the relevant guidance document from the FDA (2003).

OBJECTIVE(S)

The objective of this retrospective analysis is to uncover recent trends in the design and conduct of hepatic PK studies, based on a 3-year review of novel drugs approved by the FDA and of hepatic studies registered in *ClinicalTrials.gov* (*CT.gov*).

METHOD(S)

New Drug Application (NDA) review:

- Novel drugs approved by the FDA from 2016 to 2018 were searched to gather information on HI studies that were conducted.
- Only small molecules with significant systemic exposure were retained.

CT.gov survey:

- Hepatic PK studies first registered between 01-JAN-2016 and 31-DEC-2018 were retrieved using the search terms “hepatic impairment”, “healthy”, and “Phase I”.

Elements reviewed included the following:

- stages of HI: normal (NL), mild (MLD), moderate (MOD), severe (SEV);
- type of study designs used (e.g., full [NL, MLD, MOD, SEV], reduced [NL,MOD], or adaptive design);
- use of Population PK (PopPK) approach to assess the effect of HI on PK (only for NDA review);
- post-marketing request (PMR) for a dedicated HI study (only for NDA review).

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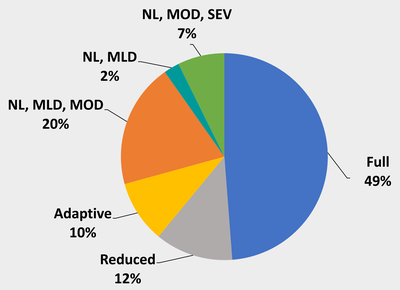
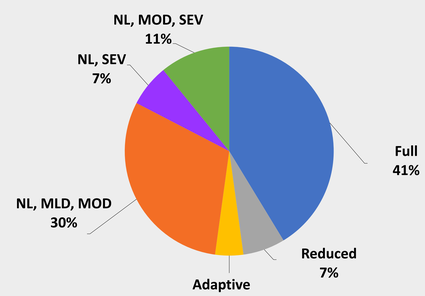
RESULT(S)

Dedicated HI studies: type of study designs

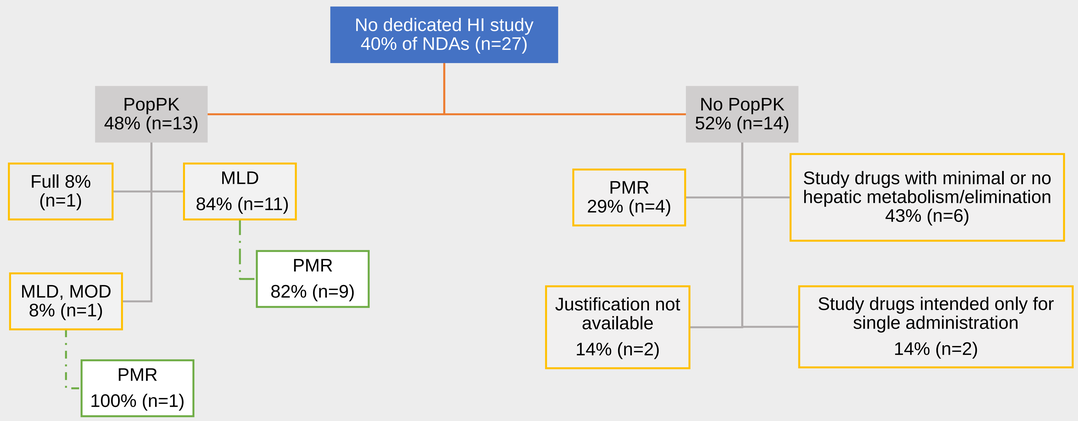
NDA review (n=41)



CT.gov survey (n=46)



NDAs with no dedicated HI studies



Description of the dataset

NDA review:

- A total of 68 NDAs were retained and reviewed.
- A dedicated HI study was conducted in 60% of those NDAs.

CT.gov survey:

- 46 studies were retained in *CT.gov* survey.

Use of PopPK approach

- A PopPK approach was used in 23 out of 68 NDAs.
- 13 cases used PopPK in absence of a dedicated HI study:
  - Mainly in oncology (n=11);
  - A PMR was requested in the majority of these cases.
- Occasionally, PopPK supported a dedicated study (n=10).
- Most PopPK included only MLD HI patients.

DISCUSSION

General trends in study designs in both databases

- 88% of dedicated HI studies were conducted under single-dose conditions (as opposed to a multiple-dose approach).
- An average of 8 subjects per cohort was targeted.
- When an adaptive design was used, it mainly consisted of two stages:
  - NL with MOD, with or without MLD;
  - Optional stage with SEV, with or without MLD.
- Reduced design:
  - The FDA guidance defines a reduced design by the inclusion of NL+MOD.
  - Our results suggest that this approach is rarely used.
  - However, it is possible that studies were initiated with MOD, then completed with other HI, similar to an adaptive approach.

HI Classification

- In dedicated studies, Child-Pugh Classification was always used, whenever information was available.
- In PopPK analysis, HI criteria defined by the National Cancer Institute Organ Dysfunction Working Group was rather used.

Labeling considerations

- Whenever a HI condition was not assessed (by a dedicated study or PopPK analysis), labeling included the following, depending on the PK results of the HI conditions studied:
  - Not studied and/or not recommended;
  - Contraindicated.

Reason for PMR for a dedicated HI study

- After PopPK analysis, PMR was done to determine if dose adjustments were needed in MOD and SEV.
- A PMR was requested in absence of PopPK, because of involvement of liver metabolism and/or elimination, or if metabolism was unknown.

CONCLUSION(S)

- Our NDA and *CT.gov* review showed that dedicated HI studies consisted mainly of full designs or studies that included at least MOD HI patients.
- A quite high proportion of NDAs did not include a dedicated HI study. However, this resulted in a PMR in about half of those cases.
- The use of PopPK analysis was quite prevalent, but could not replace a dedicated HI study, as only MLD HI was generally included.