

Dúvidas

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Arquivo

Ensaaios Fase 0 e Fase 1

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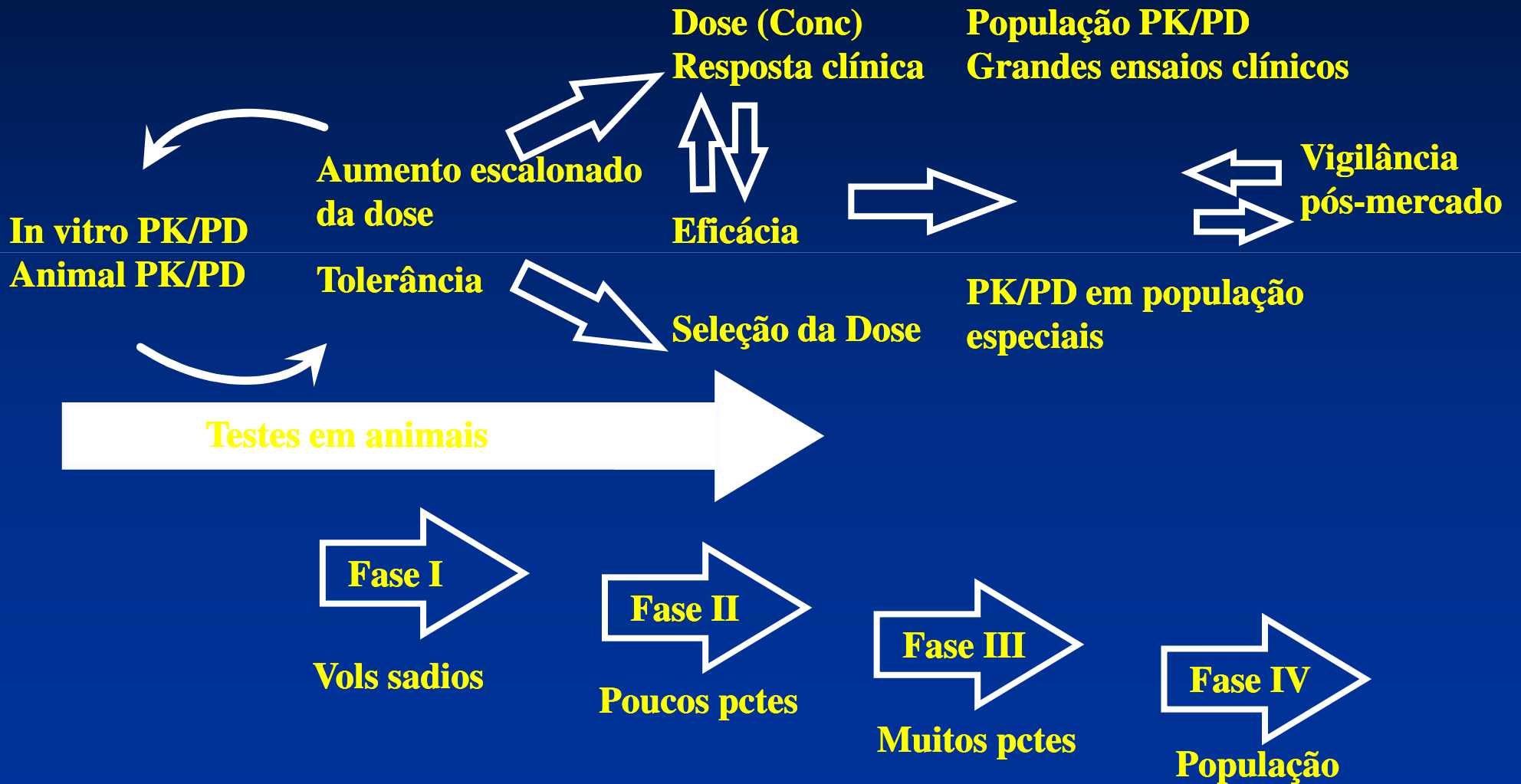
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Desenvolvimento de um Medicamento

Testes Pré-clínicos

Testes Clínicos (Humanas)



Livro de Daniel (capítulo I)

⁸Ora Daniel tomou a firme decisão de não se contaminar com as iguarias do rei e o vinho que era sua bebida. Fez um pedido ao preposto do pessoal para não ter de se contaminar, ⁹e Deus concedeu a Daniel graça e favor diante do preposto do pessoal. ¹⁰O preposto do pessoal disse a Daniel: “Temo que o rei, meu senhor, que fixou vossa alimentação e vossa bebida, vos veja de rostos mais abatidos que os dos jovens de vossa idade, e que vós me torneis culpado do preço de minha cabeça diante do rei”. ¹¹Daniel disse ao guarda^k que o preposto do pessoal encarregara de Daniel, Hananiá, Mishael e Azariá: ¹²“Põe teus servos à prova durante dez dias. Que nos sejam dados legumes para comer e água para beber. ¹³Depois olharás para nosso rosto e o rosto desses moços que comem das iguarias do rei; e age para com teus servos segundo o que vires!” ¹⁴Ele lhes deu ouvido e um prazo de dez dias, viu-se que eles tinham melhor aparência do que todos os jovens que comiam das iguarias do rei.

Farmacologia Clínica

- Avaliação de novas entidades químicas em humanos (primeira administração em humanos)
- Estudos de biodisponibilidade/bioequivalência
- Estudos de toxicologia clínica (fitoterápicos)
- Desenvolvimento de estudos farmacodinâmicos em humanos
- Desenho e condução de estudos fase II, fase III e fase IV juntamente com outras especialidades

Farmacologia Clínica

- Apesar de ser considerada *Pedra de Toque* para desenvolvimento da indústria farmacêutica, a Farmacologia Clínica não é considerada especialidade médica em nosso meio

Testes Pré-clínicos para Fase I (dose única)

- **Testes in vitro – mutagenicidade (Ames)**
- **Testes in vivo – duas espécies animais (uma não roedora) por duas semanas**

Testes Pré-clínicos para Fase I (dose múltipla)

- **Testes in vitro – mutagenicidade (Ames)**
- **Testes in vivo – duas espécies animais (uma não roedora) por quatro semanas**

Testes Clínicos

- **Fase 0 – voluntários sadios (microdosagem) – não é regulatória**
- **Fase I – voluntários sadios**
- **Fase II – pacientes para prova conceitual**
- **Fase III – grande número de pacientes – estudos multicêntricos**
- **Fase IV – vigilância pós-mercado – pesquisa sobre novas indicações**

Detecção de reações adversas

Incidência esperada de uma reação adversa	Número de pacientes necessários para detecção do evento		
	1 evento	2 eventos	3 eventos
1 em 100	300	480	650
1 em 200	600	960	1.300
1 em 1.000	3.000	4.800	6.500
1 em 2.000	6.000	9.600	13.000
1 em 10.000	30.000	48.000	65.000

Phase I Study

- Safety
- Tolerability
- Pharmacokinetic properties
- Pharmacodynamic effects

Phase I – Safety

- Does the drug produce any potentially dangerous effects, e.g. on cardiovascular, respiratory, hepatic or renal function?

Phase I – Tolerability

- Does the drug produce any unpleasant symptoms, e.g., headache, nausea, drowsiness?

Phase I – Pharmacokinetic properties

- Is the drug well absorbed? What is the time course of the plasma concentration? Is there evidence of accumulation or non-linear kinetics?

Phase I – Pharmacodynamic effects

- Does a novel analgesic compound block experimentally induced pain in humans?
How does the effect vary with dose?

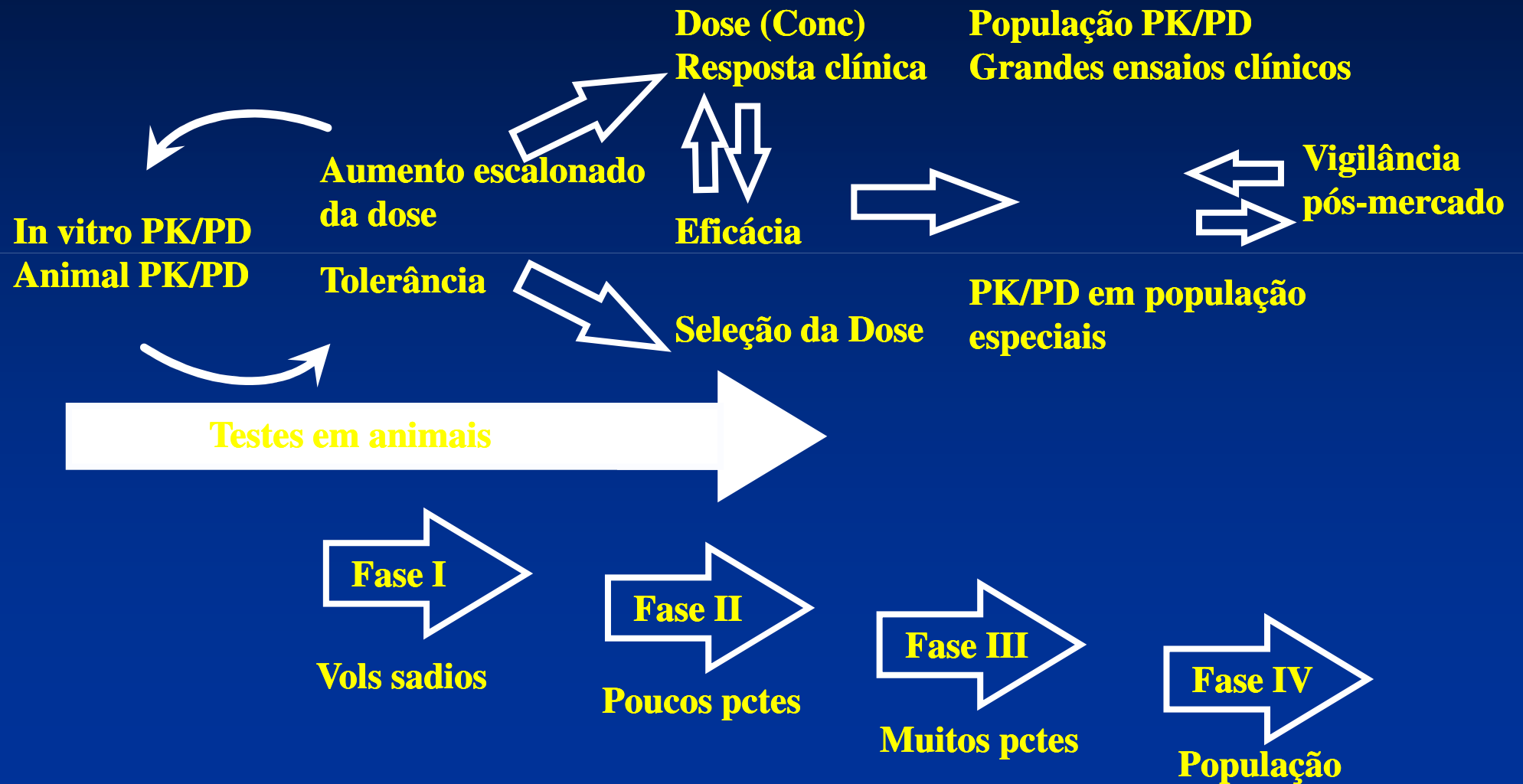
Phase I Studies

- Generally performed in a small number of healthy paid volunteers (normally 20-80).

Desenvolvimento de um Medicamento

Testes Pré-clínicos

Testes Clínicos (Humanas)



What are the advantages of conducting a Phase 0 trial?

Due to their design, Phase 0 trials can be conducted in less time with fewer patients than Phase I trials. By conducting a Phase 0 trial on a particular drug, the process for Phase I and II trials on that drug is accelerated. Additionally, because Phase 0 trials study how the body reacts to the drug and how the drug acts in the body, if a drug is found to react poorly or to have serious side effects, the testing for that drug can be stopped sooner, without the additional expense of further trials. As a limited number of low doses of drug are given in a Phase 0 trial, the risk to the participant is minimal, if any.

Additional benefits of Phase 0 trials

- Because the toxicology testing required prior to initiating Phase 0 clinical trials is reduced due to the low doses of drug used, these trials can be initiated substantially sooner than the standard Phase 1 study.
- Phase 0 trials could facilitate rational drug selection, identify therapeutic failures early, and compress timelines for anticancer drug development.
- Phase 0 trials provide initial rationale and guiding principles for further drug development based on studies in humans (rather than xenografts, where tissues of one species are transplanted to another species).
- Phase 0 trials that focus on extensively characterizing how a drug works and whether it hits its intended target (including molecular imaging studies) in a limited number of patients could yield results that would optimally inform and expedite the subsequent development of molecularly-targeted agents.

Additional benefits of Phase 0

- The results of Phase 0 trials can improve the efficiency and chance of success of subsequent trials.
- Phase 0 trials could help to evaluate the effects of an agent at the molecular level, select the lead agent from a group of compounds, and assist in optimizing the selection of the starting dose for subsequent studies. In addition, these studies can aid in developing reasonable dose escalation schedules, whereby doses of a drug are slowly increased over time in order to find the highest dose with an acceptable level of adverse side effects in the patient.

Phase 0 for which drugs?

Phase 0 trials are useful for testing targeted therapeutic drugs with wide therapeutic indexes (i.e., have a desired effect on the target without significant side effects at certain doses), as well as drugs which require development of biomarkers which may be useful for future studies. Most conventional chemotherapy drugs currently on the market have a narrow range of efficacy, or therapeutic index (i.e., doses that are effective are close to the level of doses that cause side effects). Phase 0 trials are not appropriate for drugs that have very narrow therapeutic indexes.

What are some different types of Phase 0 trials?

There are several different types of phase 0 trials, ranging from those that examine new drugs to those that test new imaging agents. Some examples include:

- Testing to see if a new drug that was developed in the lab can bind to, and inhibit, its target in humans
- Provide PD and PK data prior to definitive testing in more people
- Refine what type of biomarker is most effective using tumor tissue
- Determine which of two agents is the most promising
- Using a variety of novel imaging technologies, determine the extent of drug that is distributed in the body and whether it effectively acts upon its target

What are the standards for a Phase 0 trial?

- Validating targets or biomarkers in preclinical models and then in human tissue prior to initiating the clinical trial
- Reproducibility across labs and technicians of the assay used to measure the effect of the drug on the target
- Defining standard operating procedures for handling of tissues and biospecimens prior to initiating the clinical trial
- Demonstrating drug target or biomarker effect in preclinical models
- Determining the relationship between the pharmacodynamics and the pharmacokinetics.

Oportunidades/Dificuldades no Brasil

Fatores que tem importância fundamental na seleção do centro onde o estudo clínico deverá ser feito é a qualidade científica do investigador principal e a agilidade que o centro apresenta para a realização do estudo (aprovação do protocolo pelas instâncias necessárias, importação da medicação, etc).

