Clinical Trials in Cardiovascular Pharmacology in Argentina Between 2006 and 2010

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ABSTRACT

We conducted a survey of pharmacological studies in the cardiovascular area to analyze the characteristics of clinical trials of cardiovascular diseases sponsored by pharmaceutical companies in Argentina. The studies included had been authorized by the ANMAT between 2006 and 2010. The information was retrieved from the ANMAT database. Of 1003 trials approved over that period, 120 (11.9%) belonged to the cardiovascular area. The number of studies decreased between 2006 and 2010 (r=0.79) as opposed to the increase observed in the number of clinical trials in other specialties. A total of 120 studies were analyzed; 68.3% were trials on hypertension, coronary artery disease, peripheral vascular disease or atrial fibrillation. Eighty seven percent of the participant centers were private institutions and only 13% were community- or public hospitals. Almost all the studies corresponded to clinical trials in phase II and III. Only two bioethics committees were responsible for the approval of almost 95% of trials. In conclusion, we found a reduction in the absolute and relative number of cardiovascular studies compared to other specialties. Nevertheless, Argentina remains in the second place behind Brazil in the number of clinical trials in the cardiovascular area, although the participation of clinical research organizations was higher and that of public hospitals was very low. The fact that only two bioethics committees were responsible for the approval of most studies might prevent an adequate monitoring of study outcomes.

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Key words > Clinical Trial - Cardiology - Argentina - Bioethics

Abbreviations >

AANMAT	National Administration of Drugs, Food and Medical Technology
NIH	National Institutes of Health
CRO	Clinical Research Organization

Clinical trials sponsored by pharmaceutical companies are steadily increasing in emerging countries. (1) This tendency has been explained by the greater diffusion of medical knowledge and the improvement in regional health services, although it has also been associated to some negative aspects such as more flexible ethical and regulatory controls and a less informed population. (2,3) Cardiovascular research has long been performed by the argentine cardiology community. However, its current development and extent is unknown. Data on the growth pattern of clinical trials and distribution of involved centers, as well as the information on the sponsors and responsible bioethical committees have only become public after the National Administration of Drugs, Food and Medical Technology (ANMAT) created a public access database available on www.anmat.gov.ar. However, this information is scarcely known and its diffusion would bring clarity to clinical research sponsored by pharmaceutical companies.

The purpose of this work was thus to analyze the characteristics of cardiovascular clinical trials sponsored by pharmaceutical companies in Argentina, in order to study their temporal evolution and identify the participants contributing to their development.

METHODS

A survey of clinical trials in cardiovascular pharmacology authorized by ANMAT of Argentina was made between January 1, 2006 and December 31, 2010. The information was retrieved from the ANMAT database. The data included the ANMAT registration number, date of trial approval and initiation, study type and phase, purpose and design of the study, number of participating centers, involved bioethics committee and laboratory or company sponsoring the study. The survey strategy included the topic units "cardiology"

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and "cardiovascular" comprising all clinical trials related to cardiology itself and cerebrovascular and peripheral vascular diseases. To monitor the results obtained from the ANMAT database, and additional survey was performed in the National Institutes of Health (NIH) International Clinical Trials Registry database, available on www.clinicaltrials.gov. This survey revealed 13% under-registration of Argentine clinical trials with respect to those registered in ANMAT (104 vs. 120 cardiovascular trials, respectively, over the same time period). Thus, the national database was used in this report. Moreover, the quality of the information registered in the NIH database has been questioned by some authors (4). Nevertheless, due to lack of other sources of information, the NIH database was employed to compare the number of clinical trials in cardiovascular pharmacology conducted in Latin American countries. In this case it was assumed that under-registration of clinical trials would equally affect all the studied countries.

RESULTS

From a total number of 1003 pharmacological clinical trials approved by ANMAT between 2006 and 2010, 120 (11.9%) belonged to cardiovascular diseases. Figure 1 shows the number of new trials incorporated each year (r =0.79). Eighty two out of 120 analyzed trials (68.3%) were on hypertension, coronary disease, peripheral vascular disease or atrial fibrillation. The distribution of all cardiovascular topics is shown in Table 1 (a) and the distribution of clinical phases for all the studies is summarized in Table 1 (b), where a notorious absence of phase I trials is observed. Table 2 (a) lists the laboratories or companies sponsoring the studies, excluding sponsors with only one clinical trial in the country, and Table 2 (b) shows the bioethics committees involved in protocol approval.

Figure 2 represents the frequency distribution of centers participating in different trials. For example, only one center participated in 62 studies, two centers in 20 studies, and so on. Three hundred and thirty seven out of 389 centers (86.6%) were private institutions and the rest (52/389) municipal and provincial community or public hospitals.

The NIH database was used to build the map (Figure 3) depicting the number of trials in cardiovascular diseases conducted in each Latin American country compared with those performed in Argentina between 2006 and 2010.

DISCUSSION

Clinical trial registries are used to provide transparency to studies and their results. This work described the characteristics of cardiovascular clinical trials sponsored by pharmaceutical companies, registered in the ANMAT public database. The most frequent research areas were hypertension and coronary disease and virtually all the studies corresponded to phases II and III of clinical research. One of the main reasons for globalization or extension of pharmacological clinical trials to emerging countries is the need to rapidly enroll a sufficient number of patients in order to reduce the time of putting the drug in the market.

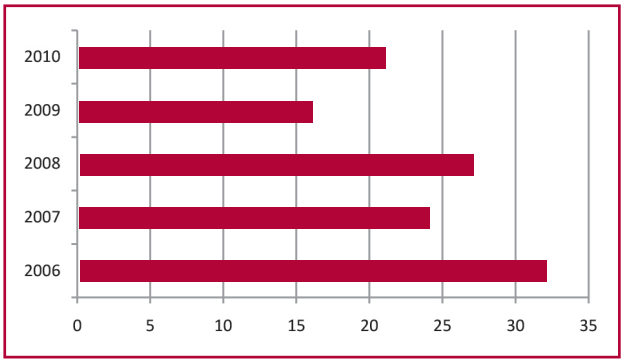

Fig. 1. Number of cardiovascular clinical trials approved by ANMAT per year.

Table 1. Number of Studies per cardiovascular topic (a) and study phase distribution (b)

a

Cardiovascular topics	n	(%)
Arterial hypertension	28	23,3%
Coronary disease	26	21,7%
Peripheral vascular disease	15	12,5%
Atrial fibrillation	14	11,7%
Pulmonary hypertension	9	7,5%
Acute heart failure	7	5,8%
Cardiovascular mortality	6	5,0%
Chronic heart failure	4	3,3%
Stroke	2	1,7%
Hypercolesterolemia	2	1,7%
Others	7	5,8%
Total	120	100%

b

Study phase	n	(%)
I	0	0%
II	30	25,0%
III	86	71,7%
IV	4	3,3%
Total	120	100%

Moreover, since drug approval in phase III requires large samples of patients, this type of study is also the one that predominates locally.

The analysis of cardiovascular trials approved by ANMAT showed that their absolute number decreased between 2006 and 2010 (r = 0.79), as opposed to the increase observed in the number of clinical trials corresponding to other specialties.(5) The selection of a country to participate in a clinical trial sponsored by pharmaceutical companies depends on its capacity or ability to recruit patients. Up to a certain extent, eligibility is also related to the time of approval required by the regulatory authorities of the country, which is sometimes only justifiable in mega-trials or in the case of rare diseases. Nevertheless, compared with the rest of Latin American countries, Argentina occupied the second place behind Brazil in the number

Table 2. Participation of pharmaceutical laboratories and companies sponsoring the clinical trials (a) and bioethics committees involved in protocol approval (b).

a

Sponsor	n	(%)
Novartis	16	13,3%
Sanofi Aventis	10	8,3%
Kendle Argentina	9	7,5%
Takeda Global	9	7,5%
Boehringer	6	5,0%
Bristol Myers Squibb	5	4,2%
Pfizer	5	4,2%
Bayer	5	4,2%
Astellas Pharma	4	3,3%
PPD Argentina	4	3,3%
Servier	4	3,3%
Schering Plough	4	3,3%
Quintiles Arg	4	3,3%
Merck	3	2,5%
Daiichi Sankyo INC	3	2,5%
Otros	29	24,2%
Total	120	100%

b

Bioethics committee	n	(%)
Hospital	8	6,7%
Foglia-Barclay	18	15,0%
Zieher	94	78,3%
Total	120	100%

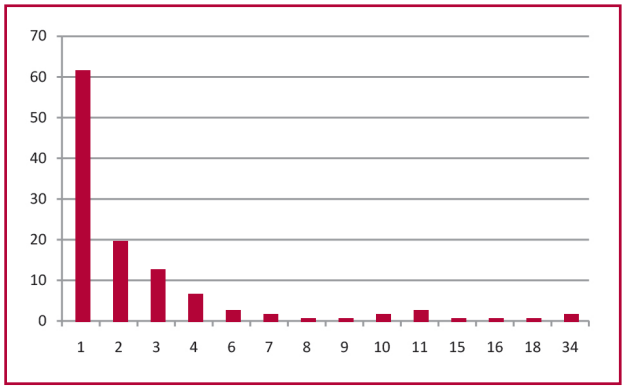

Fig. 2. Distribution of the number of participating centers per clinical trial (total: 389 centers)

of clinical trials in cardiovascular pharmacology performed between 2006 y 2010 (see Figure 3).

The local participation of sponsor laboratories was similar to that in the rest of emerging countries conducting clinical trials, led by Novartis and Sanofi-Aventis. (1) It is worth mentioning that clinical research organizations (CRO) participated in approximately 22% of the cardiovascular trials conducted in that period. Another noteworthy factor is the concentration of clinical trial approval in two bioethics committees, one of which was responsible for the approval of more than 75% trials. Taking into account that, to a certain point, a bioethics committee should monitor the course of clinical trials to control the implementation of established ethical guidelines and patient safety, the need of a vast monitoring capacity would only be met by a small number of committees. It would be desirable to have a more equitably balanced protocol distribution in the future. In effect, the scarce participation of hospital committees is due to the small participation of public hospitals in clinical trials sponsored by pharmaceutical companies in the last years. However, when a public hospital participates in a clinical trial, the involvement of its bioethical committee is mandatory for protocol approval, even though this participation might not be reflected in ANMAT registries. Absence of a clear regulation for the conduction of pharmacological clinical trials in the public sector has displaced most protocols to the private sector. Although there might be some limitations in the quality of information included in the ANMAT database, either due to error or redundancy, the comparison with the NIH clinical trials registry (6) demonstrated its consistency.

In conclusion, the public access of the ANMAT clinical trial registries clarifies a sensitive activity such as clinical research sponsored by pharmaceutical companies. Specifically, there has been a reduction in the absolute and relative number of studies in the

Fig. 2. Map indicating the number of clinical trials in cardiovascular pharmacology conducted in each Latin American country between 2006 and 2010 (retrieved from the NIH database, www.clinicaltrials.gov). Data for Argentina indicates 13% sub-registration with respect to the national information provided by ANMAT. A similar sub-registration is considered for the rest of the data.

cardiovascular area compared to other specialties. Nevertheless, Argentina remains in the second place behind Brazil in the number of cardiovascular clinical trials, with a sponsor distribution similar to that of the rest of emerging countries but with a higher participation of CROs and a smaller participation of community and public hospitals. In conclusion, we emphasize the need of expanding the number of bioethics committees to approve protocols, since the concentration of decisions in a few hands might prevent an adequate monitoring of study outcomes.

RESUMEN

Informe sobre los ensayos clínicos farmacológicos en cardiología realizados en la Argentina entre 2006 y 2010

Con el objetivo de analizar las características de los ensayos clínicos farmacológicos patrocinados por la industria en el área de las enfermedades cardiovasculares en la Argentina, se efectuó una búsqueda de los estudios farmacológicos realizados en el área de la cardiología, autorizados por la ANMAT entre 2006 y 2010, mediante la base de datos pública de dicho organismo. De 1.003 ensayos aprobados en ese período, 120 (11,9%) pertenecían al área de las enfermedades cardiovasculares. Se observó una reducción en términos absolutos del número de estudios entre 2006 y 2010 (r = 0,79), tendencia que se contrapuso al aumento de los ensayos clínicos observado en otras especialidades. De los 120 estudios analizados, el 68,3% pertenecían a ensayos sobre hipertensión, enfermedad coronaria, enfermedad vascular periférica o fibrilación auricular. Del total de centros participantes, el 87% correspondió a entidades privadas y sólo el 13% a hospitales comunitarios o públicos. Casi la totalidad de los estudios correspondieron a las fases II y III de investigación clínica y sólo dos comités de bioética fueron responsables de la aprobación de casi el 95% de los ensayos. En conclusión, los estudios del área cardiovascular han mostrado una reducción en su número absoluto y relativo con respecto a otras áreas. Pese a ello, la Argentina mantiene el segundo puesto en cantidad de ensayos cardiovasculares detrás de Brasil, aunque con una injerencia mayor de las organizaciones de investigación clínica y una participación menor de los hospitales públicos. La alta concentración de aprobaciones de estudios en sólo dos comités de bioética impediría un control adecuado de la evolución de los protocolos.

Palabras clave > Ensayo clínico - Cardiología - Argentina - Bioética

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