



SPECIAL ARTICLE

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Mapping the clinical pharmacokinetics and pharmacogenetic units operating in Spanish hospitals

Mapa de unidades de farmacocinética y farmacogenética clínica en España

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Abstract

Objective: The goal of this article is to analyze the situation of pharmacokinetics and pharmacogenetics units in the pharmacy departments of Spanish hospitals, evaluate their development both in the clinical and educational areas, and draw up a map reflecting their current status.

Method: A 29-item survey structured in five blocks was designed with general questions about the respondents' hospital and the clinical and educational activities carried out by their pharmacy department, in the fields of both pharmacokinetics and pharmacogenetics.

Results: Sixty-nine hospitals answered the survey. The highest response rates corresponded to Catalonia, the Valencia region and Andalusia. The drug families subject to closest monitoring were classic antibiotics (93%), digoxin (57%), classic antiepileptics (51%) and biologicals (43%). The most frequently used computer programs included PKS and NONMEM (93% and 22% of hospitals, respectively). Regarding training in pharmacokinetics, second year residents were those who most frequently rotated through the pharmacokinetics unit (40%), while 44% of those units allowed external residents. As far as pharmacogenetics is concerned, in 42% of hospitals that engaged in pharmacogenetic work, the department in charge was pharmacy. The most frequent specialties covered were hemato-oncology (72%) and psychiatry (15%). Twenty-four percent of hospitals offered rotations through their pharmacogenetics unit but only seven of them allowed external residents.

Conclusions: The results of the survey showed an increase in the performance of pharmacokinetic and pharmacogenetic activities by Spanish hospital pharmacies as compared with the data from a 2009 baseline

Resumen

Objetivo: Dar a conocer la actividad asistencial y docente de las unidades de farmacocinética y farmacogenética de los servicios de farmacia hospitalaria españoles y elaborar un mapa que refleje la situación actual.

Método: Se diseñó una encuesta de 29 preguntas estructuradas en cinco bloques: datos generales del hospital e información sobre la actividad asistencial y docente, tanto en el área de farmacocinética como de farmacogenética en los servicios de farmacia hospitalaria.

Resultados: Respondieron la encuesta 69 hospitales. Las regiones geográficas con mayor número de respuestas fueron Cataluña, Comunidad Valenciana y Andalucía. Los grupos farmacológicos que más se monitorizaron fueron los antibióticos clásicos (vancomicina y aminoglucósidos) (93%), digoxina (57%), antiepilépticos clásicos (51%) y biológicos (43%). Los programas informáticos que con más frecuencia se utilizaban fueron PKS y NONMEM, con un 93% y 22%, respectivamente. Respecto a la docencia en farmacocinética, fue el segundo año de residencia cuando la mayoría de los farmacéuticos internos residentes rotaban por el área (40%) y un 44% de las unidades permitían rotantes externos. El responsable de la farmacogenética era el servicio de farmacia hospitalario en un 43% de los casos. Los ámbitos más frecuentes fueron oncohematología (72%) y psiquiatría (15%). Un 24% de los hospitales ofrecían rotación por la unidad de farmacogenética y sólo 7 servicios de farmacia ofertaron rotaciones externas.

Conclusiones: Los resultados de la encuesta mostraron un incremento en la realización de actividades de farmacocinética y farmacogenética en los servicios de farmacia hospitalaria comparados con los datos de la encuesta

KEYWORDS

Pharmacokinetics; Pharmacogenetics; Surveys and questionnaires; Pharmacy department, hospital, training.

PALABRAS CLAVE

Farmacocinética; Farmacogenética, Encuestas y cuestionarios; Servicio de farmacia hospitalaria, docencia.



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survey, with many hospitals introducing the performance of therapeutic drug monitoring of non-classical antibiotics, immunosuppressants and biologics. However, the percentage of hospitals that follow the ideal model based on analytical determinations and pharmacokinetic reporting has decreased the data obtained served as a basis to create an updated map of the pharmacokinetics and pharmacogenetics units operating in Spanish hospital pharmacy departments. This map, available at <http://bit.ly/mapaPKGen>, will be very useful to facilitate the training of residents in these disciplines and will help promote the development of pharmacokinetic and pharmacogenetic activities among hospital pharmacists.

Introduction

Clinical Pharmacokinetics (PK) is a practical discipline whose origins go back to the early 1970's. Until then it had been an academic discipline applied only by researchers. In Spain, it was consolidated in the 1980s as an essential activity for hospital pharmacists. The factors that have made the greatest contribution to its expansion in the clinical setting include the development of its theoretical and practical foundations, the availability of automated analytical methods for establishing PK profiles, and the greater accessibility to computer programs, including dosage adjustment systems. However, the expansion of PK has not been as dramatic as expected, with only a small number of hospitals incorporating PK units. A similar situation has been experienced by other countries too^{2,3}.

PK can be defined as the application of PK and pharmacodynamic (PD) principles to promote safe and effective pharmacotherapeutic patient management. The ultimate goal is adjustment or individualization of drug dosage based on plasma or blood drug concentrations and on the patient's clinical situation. PK monitoring therefore consists of two steps, determining a drug's serum concentrations and interpreting the data in a PK report. The reliability of this strategy depends firstly on the quality of the information obtained, and secondly on the appropriate use of PK/PD criteria. In this regard, the preparation of the PK report is the most important stage of PK and requires precise academic training in this discipline^{4,5}.

The contribution of PK to the improvement of therapeutic outcomes has led to the creation of the so-called Clinical Pharmacokinetics Units (CPU). Their implementation within hospital pharmacy departments (HPDs) in Spanish hospitals has been based on different models. The optimal model is to perform an analytical determination of serum drug concentration in order to ensure an adequate interpretation of the results when preparing the above-mentioned pharmacokinetic report. It could also be possible to just prepare the pharmacokinetic report, but the main disadvantage of this approach is the lack of information about quality control procedures applied during the analytical phase, which is indispensable to the interpret results that may be anomalous or inconsistent with the clinical situation of the patient. The third option, which is not implemented by many HPDs, is to perform only the analytical determination, reporting only the data corresponding to reference therapeutic window. The efficiency of this last approach is questionable, and generates a series of costs with no real clinical benefit⁶.

A discipline that is closely linked to PK is pharmacogenetics (PG). Although the concept of PG emerged in the 1950s to take into consideration the influence of genetic inheritance on the organism's response to different drugs, it was in the early years of the 21st century that it began to be adopted as an affordable reality by large hospitals in Spain. This heralded an important conceptual change in the approach to pharmacotherapeutic treatment. PG is a discipline that studies the influence of variations in the DNA sequence on the efficacy and safety of pharmacological treatment. The main purpose is the identification and characterization of polymorphisms of certain genes, their correlation with clinical results and, finally, the development of genetic tests that may predict the patient's clinical response and/or the toxicity profile of a given drug⁵. It is important to quantify the percentage of the variability observed in the exposure to a given drug that may be attributable to genetics. This means that PG should be considered an ally of PK. Although it is an indisputable aid in decision making regarding the establishment of a pharmacological treatment, it should never be only tool used for dosage adjustment⁷. PG knowledge is currently being successfully applied in some areas of

basal de 2009. Se inició la realización de monitorización terapéutica de biológicos, inmunosupresores y antibióticos no clásicos. Sin embargo, ha disminuido el porcentaje de hospitales que aplican el modelo ideal basado en la realización de determinación analítica e informe farmacocinético desde farmacia. Los datos obtenidos permiten disponer de un mapa actualizado de las unidades de farmacocinética y farmacogenética clínicas en los servicios de farmacia hospitalaria españoles. Esta información se encuentra disponible en <http://bit.ly/mapaPKGen> y será de gran utilidad para facilitar la formación de nuestros residentes en estas disciplinas y ayudará a promover su desarrollo entre los farmacéuticos de hospital.

medicine such as oncology, psychiatry, HIV, cardiovascular therapy and transplants. Its widespread implementation requires the setting up of multi-disciplinary teams, and HPDs can play an essential role in the integration of PG into healthcare routines. There are, however, major barriers to the implementation of PG by HPDs at a large scale. These include the translation of research into clinical practice, the difficulty in selecting validated genomic biomarkers, the slow acceptance and demand of PK by clinicians, limited PK training at hospital pharmacies, the high initial cost of the infrastructure required, and the controversial cost/effectiveness ratio of PK tests⁸. Despite initial forecasts, PG has not as yet been implemented in clinical practice as widely as expected.

The Spanish clinical PK and PG group (PKgen) was established in May 2008. One of its main goals was to encourage the implementation of PK in all HPDs. To do this, it was considered essential to gain a clear understanding of the degree to which this activity had been embraced by Spanish HPDs. An initiative was launched to draw up a catalog of hospitals with a CPU, with their respective portfolios of services, their availability to accommodate external residents and their rotation times. To this end, a survey was carried out, the results of which were presented at the 54th SEFH National Congress held in Zaragoza in 2009⁹. Only 40 HPDs reported carrying out PK activities, i.e., 39% of the hospitals accredited for training. This figure was far from the proposed standard of 80% set for 2020. In addition, these 40 hospitals did not conduct pharmacokinetic monitoring of all the drugs administered. Ninety-three percent monitored antibiotics (tobramycin only 80%). 88% digoxin, 75% theophylline, 48% methotrexate, 35% lithium, 80% classical antiepileptics (phenytoin, carbamazepine, phenobarbital and valproic acid), 15% new antiepileptics, and 28% all immunosuppressants. The survey revealed two remarkable facts. One was the scarce involvement of HPDs in the teaching of this discipline (only 68% trained their own residents and only 35% [14 HPDs] also trained residents from other hospitals). The other was that only 53% (21) of HPDs had implemented most comprehensive PK model and also performed analytical drug determinations, while the remaining 48% (19 HPDs) only performed pharmacokinetic reports. Interestingly, 6 centers stated that they did not make dosing recommendations.

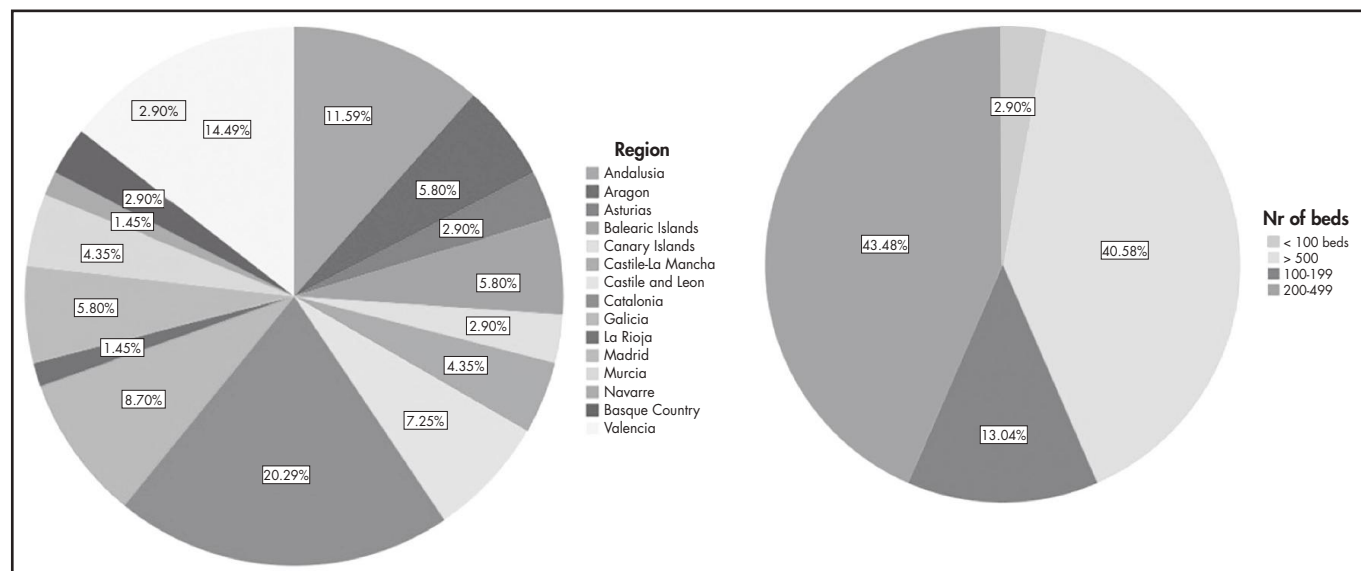
In 2012, a new survey was conducted to evaluate the situation of PG in Spanish HPDs. Thirty-two hospitals participated, of which approximately half (17 hospitals) claimed to perform PG tests, either for clinical (7 HPDs) or, for research (7 HPDs) purposes, or at least to be very interested in starting this type of activity in the near future (3 HPDs). The type of drugs analyzed in clinical tests varied from one HPD to another, although PG analyses of 5-FU (21% of HPDs surveyed), tacrolimus (14%), pegylated interferon + ribavirin (10%) and irinotecan (10%) were particularly common⁸.

A few years later, the PKgen group set about drawing up a map of the activity of the PK and PG units in Spain using a similar methodology, i.e., through a survey addressed to all HPDs. The aim was to provide an update of degree to which PK and PG had been implemented by HPDs; characterize the way in which these activities were developed in each HPD; describe the evolution of PK and PG activities over the years; and offer easily accessible and updated information on the training capacity of HPDs, which may be of use for residents wishing to be trained in these disciplines.

Methods

An online survey was sent (1 March 2021) to SEFH members. In addition, in order to maximize its reach, the survey was also publicized through

Figure 1. General characteristics of the hospitals.



the PKgen's twitter account (@GrupoPKgen_SEFH). The survey, developed using Google forms, contained 29 items and was structured into five blocks with general questions about the respondents' hospital and the clinical and educational activities carried out by the HPD, both in the field of PK and PG.

The section on clinical activities related to PK included questions on to the drugs monitored, the availability of a laboratory to determine plasma levels in the HPD, the computer programs used for dosage adjustment, and the information included in the PK report. As regards PG, questions asked whether the HPD performed genotyping and/or pharmacogenetic reporting tasks and what the scope of such activities was. As far as training in PK and PG was concerned, questions dealt with the respondents' hospital's resident training plan and its capacity to offer external rotations. Access to the survey was maintained for 3 months, during which time two reminder e-mails were sent to prospective respondents.

The results were exported to an Excel spreadsheet and possible discrepancies were analyzed. Duplicate responses were identified, and in those cases where the information collected was considered incomplete or

to contain errors of interpretation, respondents were contacted again and asked to send a corrected version.

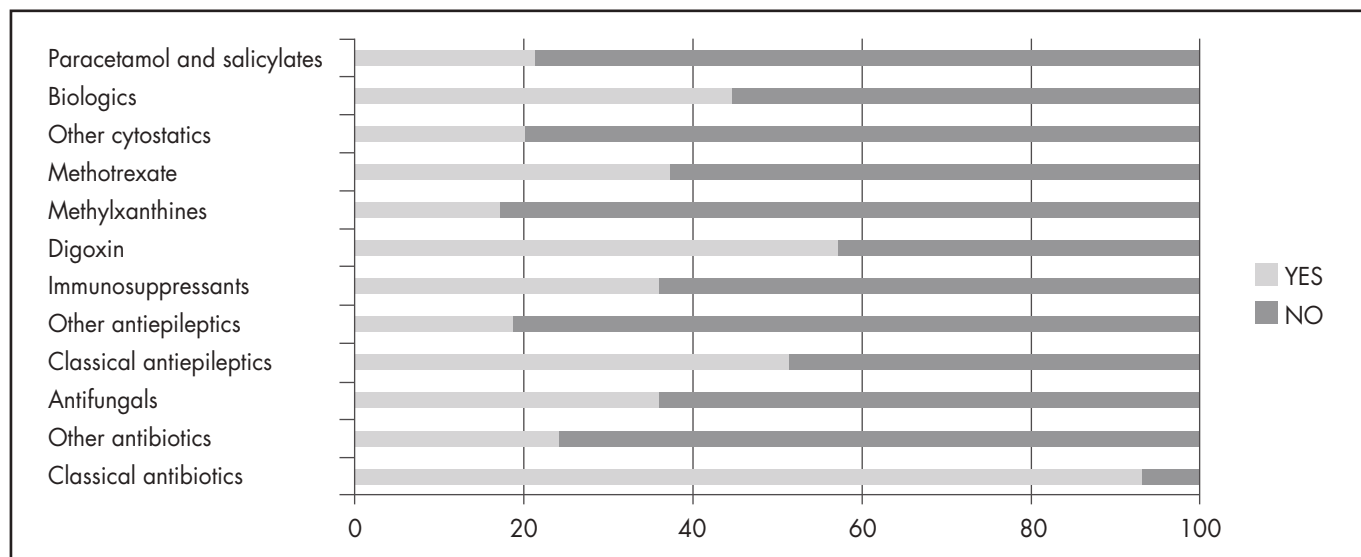
Google's My Maps application was used to create the PK and PG units map, importing responses as independent layers. The map included information on the availability of a PK laboratory in the HPD, the preparation of reports and the hospitals where clinical PG testing was performed.

Results

A total of 69 hospitals nationwide responded to the survey. Figure 1 shows the geographical distribution and size of the hospitals (expressed in number of beds). Figure 2 shows the percentage of hospitals that performed pharmacokinetic monitoring of different drug groups. Table 1 shows the portfolio of services by drug group, specifying whether CPUs had an analytical laboratory, only engaged in pharmacokinetic reporting, or performed both functions.

As regards the use of computer programs by CPUs, it should be noted that the most frequently used application for making dose adjustments by means of

Figure 2. Pharmacokinetic monitoring of different pharmacological groups.



Bayesian methods was PKS® (93% of cases); NONMEM® was used by 22% of CPUs and Monolix® by 9%. It is important to note that 25% of CPUs used Excel sheets to prepare pharmacokinetic reports for certain drugs.

As regards training in PK (Figure 3), it was observed that it was during the second year of residency when most interns rotated through this area; the average duration of rotations was 3-6 months. On the other hand, 44% of the CPUs allowed external intern rotations, with a minimum duration of 1 week and a maximum duration of 3 months.

As regards PG, of the 69 hospitals that responded to the survey, 41% (n = 28) carried out this activity and 43% (n = 12) of these had a PG unit in their HPD. Seventy-two percent applied PG testing to hemato-oncology, followed by 15% who used PG in psychiatry. It should be noted that all 12 hospitals where PG determinations were performed at the HPD prepared clinical pharmacogenetic reports. With respect to training, only 25% of the hospitals offered residents the possibility of rotating through a PG unit, with those in their third year of residency being the most active in this regard. Furthermore, only seven HPDs offered external intern rotations. PK training results are shown in figure 4.

The information was compiled in an interactive map available at <http://bit.ly/mapaPKGen> (Figure 5). The map allows differentiation between the CPUs that draw up pharmacokinetic reports, those that also measure drug plasma levels in the pharmacy and hospitals that have a PG unit their HPD.

Discussion

The survey conducted by the PKgen group in 2009 to determine the situation of PK in our country was answered by 72 Spanish HPDs. Only 40 performed PK activities, which accounted for 39% of all hospitals accredited for training⁹. Sixty-nine respondents of the current survey stated that their HPD carried out PK and/or PG healthcare activities. These figures reflect a significant growth in the number of HPDs performing PK work. Data from the *White Book of Hospital Pharmacy*¹⁰, published in 2019, show that 12% of HPDs perform plasma level determinations and 34% prepare pharmacokinetic reports. Although the 80% target established in the SEFH strategic plan is still a long way away, the trend is clearly encouraging. The degree of implementation of PK in Spain is similar to that observed in the rest of Europe. According to the 2010 survey of the European Association of Hospital Pharmacists (EAHP), 25% of HPDs performed clinical PK activities¹¹. However, significant differences were observed with respect to the situation in the United States. In its 2018 national survey, the American Society of Health-System Pharmacists (ASHP) reported that the 97% of US hospitals performed clinical PK activities. Furthermore, in 85.5% of US hospitals, it was the pharmacist who was in charge of requesting PK monitoring tests and, in 84.5% of cases, pharmacists prepared the pharmacokinetic report indicating dose adjustments required¹².

An analysis of the activity of CPUs in terms of drug families and comparing the results obtained by the survey discussed in this article with those of the baseline (2009) survey, classical antibiotics continue to be the main group of drugs monitored in Spanish hospitals. With respect to digoxin and classic antiepileptics, the number of hospitals that monitor them had remained unchanged. On the other hand, the percentage of hospitals performing therapeutic drug monitoring (TDM) of immunosuppressants and new antiepileptics has increased with respect to 2009. In addition, it is worth highlighting the new molecules that are now subject to TDM, especially biologics, antifungals and non-classical antibiotics. The implementation of TDM of biologics can be explained by the great progress made in the field of monoclonal antibody monitoring in recent years in the context of autoimmune conditions. Also noteworthy is the implementation of antifungals, which is probably the result of the publication of clinical guidelines with recommendations for TDM of those drugs^{13,14}. Finally, the great progress that has been made in the field of anti-infectives, including the new insights gained into the influence of the PK/PD profile of antibiotics in their efficacy and safety, is reflected in the percentage of hospitals that monitor the plasma levels of non-classical antibiotics such as linezolid, beta-lactams, daptomycin and colistin nowadays.

With respect to the PK/PD model, the model based on analytical determination without preparation of a report was in the minority. PK reporting without analytical determination was, on the other hand, much more frequent, especially regarding three pharmacological groups: classical antibiotics, classical antiepileptics and digoxin. Finally, the ideal model, based on performing

Table 1. Activities performed by CPUs in Spanish HPDs

Service portfolio	Activity	Frequency	Percentage (%)
Classical antibiotics (vancomycin/aminoglycosides)	DA	0	0.0
	PKR	52	75.4
	DA + PKR	12	17.4
	n.a.	5	7.2
Other antibiotics (betalactams/linezolid/daptomycin/colistin)	DA	0	0.0
	PKR	7	10.1
	DA + PKR	10	14.5
	n.a.	52	75.4
Antifungals (azoles/candins)	DA	0	0.0
	PKR	16	23.2
	DA + PKR	8	11.6
	n.a.	45	65.2
Classical antiepileptics (carbamazepine/phenytoin/phenobarbital/valproic acid)	DA	0	0.0
	PKR	24	34.8
	DA + PKR	11	15.9
	n.a.	34	49.3
Other antiepileptics (eslicarbazepine/ethosuximide/gabapentin/lamotrigine/levetiracetam)	DA	0	0.0
	PKR	6	8.7
	DA + PKR	6	8.7
	n.a.	57	82.6
Immunosuppressants (tacrolimus/everolimus/cyclosporine)	DA	1	1.4
	PKR	13	18.8
	AD + PKR	10	14.5
	n.a.	45	65.2
Digoxin	AD	0	0.0
	PKR	26	37.7
	AD + PKR	13	18.8
	n.a.	30	43.5
Methylxanthines (theophylline/caffeine)	AD	1	1.4
	PKR	4	5.8
	AD + PKR	7	10.1
	n.a.	57	82.6
Methotrexate	AD	2	2.9
	PKR	16	23.2
	AD + PKR	7	10.1
	n.a.	44	63.8
Other cytostatics	AD	1	1.4
	PKR	4	5.8
	AD + PKR	9	13.0
	n.a.	55	79.7
Biologics (adalimumab/certolizumab/infliximab/ustekinumab/vedolizumab)	AD	1	1.45
	PKR	15	21.74
	AD + PKR	14	20.29
	n.a.	39	56.52
Paracetamol and salicylates	AD	1	1.4
	PKR	5	7.2
	AD + PKR	8	11.6
	n.a.	55	79.7

AD: analytical determination; n.a.: no information available; PKR: pharmacokinetic report.

Figure 3. Training in pharmacokinetics units.

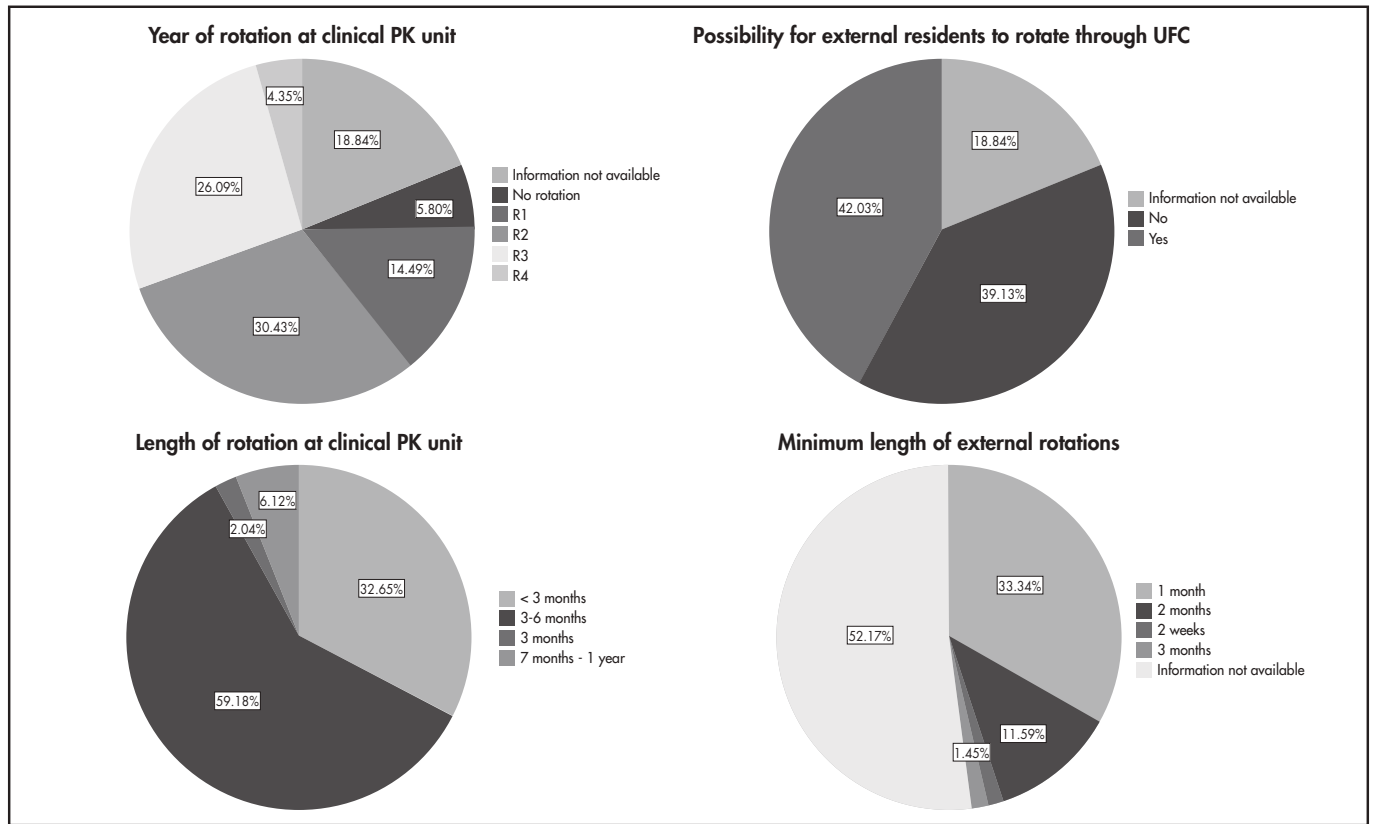


Figure 4. Training in pharmacogenetics units.

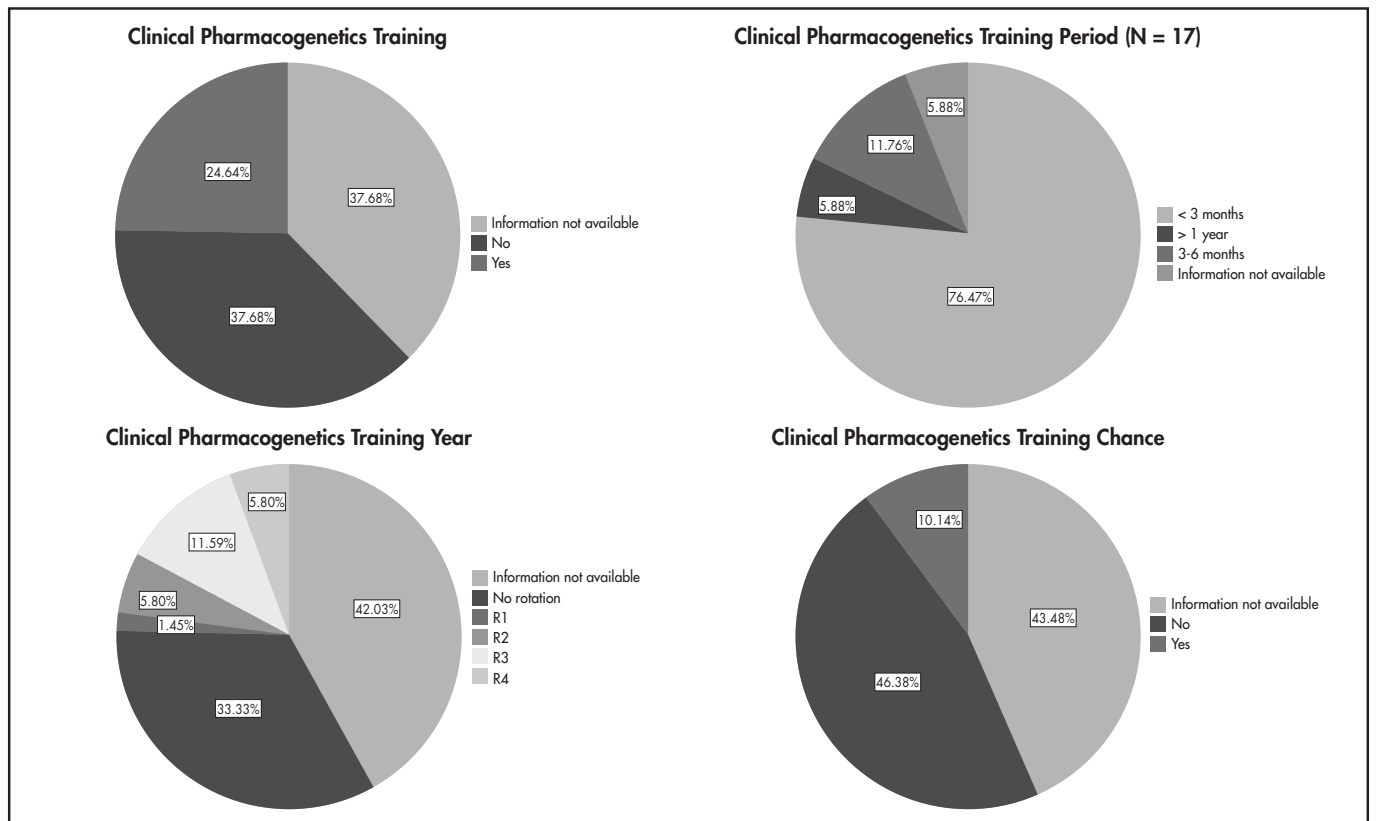
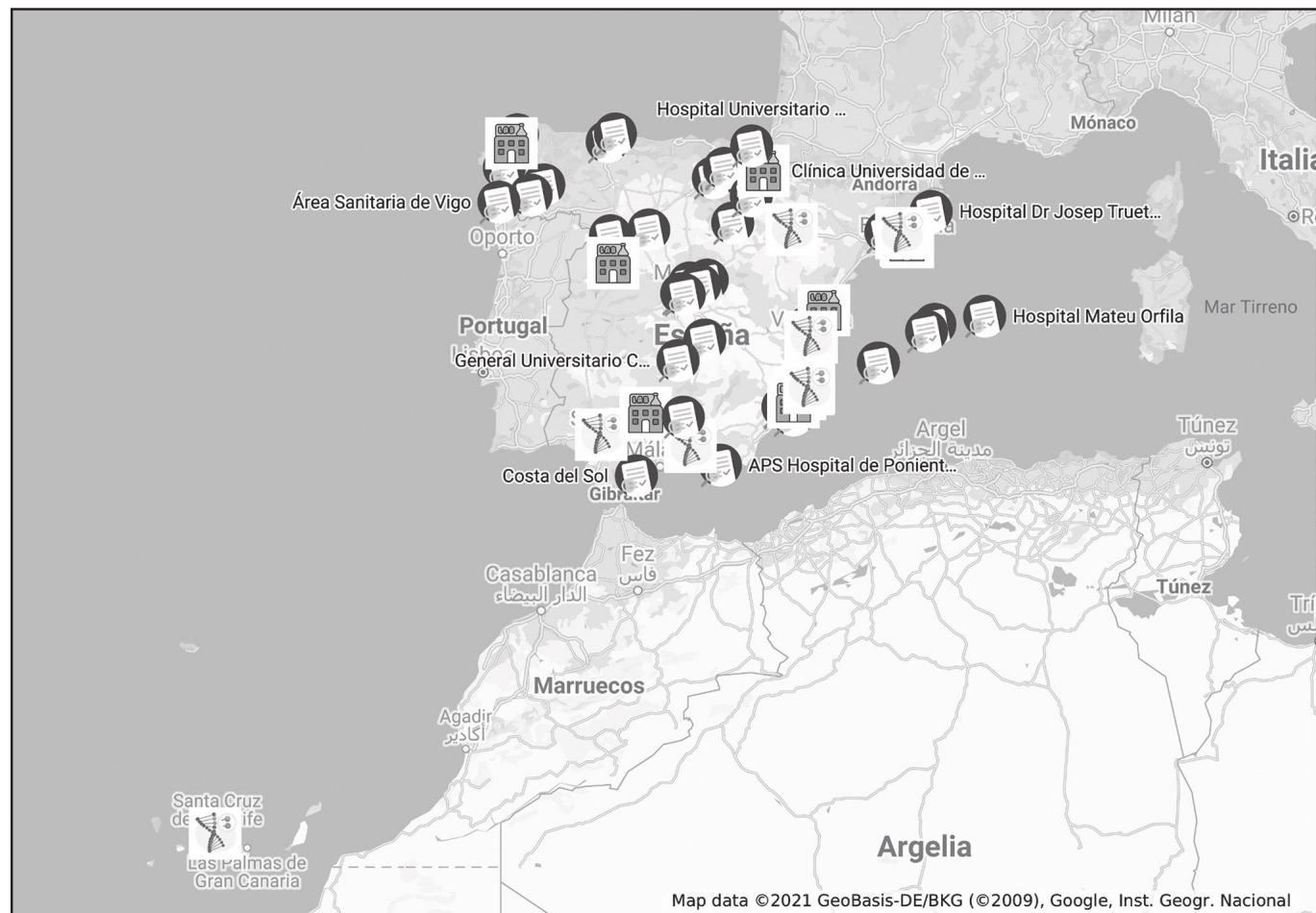


Figure 5. Pharmacokinetics and pharmacogenetics units map.

analytical determination and preparing pharmacokinetic reports prevailed in the case of drugs where TDM implementation was more recent, such as immunosuppressants, antiepileptics and non-classical antibiotics. These results may be due to the fact that inclusion of the monitoring of new drugs in the service portfolio of Spanish hospitals is largely driven by HPDs, and it is therefore HPDs that have taken the initiative in recent years in the development and implementation of TDM of new molecules in clinical practice. Despite this, a decrease was observed in the proportion of hospitals in which PK determinations and preparation of reports was performed (14%) with respect to the situation in 2009, when 53% of HPDs performed analytical determinations⁹. In this regard, the PKGen group continues to support the implementation CPUs, following the guidelines of the optimal quality model, where HPDs perform analytical determinations and steadily expand their portfolio of services.

As regards PG, an increase was observed in the number of HPDs engaging in this activity. Specifically, when comparing the results of the current survey with those of 2012, a trend was observed towards the translation of research into clinical practice. However, there is still a long way to go since 60% of the hospitals surveyed do not engage in PG activities, which is consistent with the scarce training offered to residents in that field. These results are similar to those published in the *White Book of Hospital Pharmacy*, which states that involvement of residents in PG activities is low¹⁵, and that the involvement of HPDs in PG activities is limited and to larger hospitals. The presence of hospital pharmacists specialized in genetics is still negligible in our country, especially if we compare it with the situation in other countries. According to the 2019 ASHP survey, 5% of hospitals in the US have pharmacists who recommend or schedule PG tests to assist in the drug selection and dosing process, and 4% have at least one pharmacist as an expert consultant in a clinical PG service¹². In Spain, PG is an incipient activity that should be expanded in the coming years.

The results of the survey showed an increase in the performance of PK and PG activities in HPDs, as compared to the data from the baseline survey. The therapeutic monitoring of biologics, immunosuppressants and non-classical antibiotics having been implemented since 2009. However, the percentage of hospitals applying the ideal model based on analytical determinations and preparation of pharmacokinetic reports by HPDs has decreased.

The data obtained provide an up-to-date snapshot of the situation of PK and PG units in Spanish HPDs that will be instrumental in facilitating the training of residents in these disciplines and will help promote their development.

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Conflict of interest

No conflict of interest.

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