biology and life sciences forum

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Proceedings paper

Clinical review of a polyvalent F (ab')$_2$ antivenom (Inoserp™ PAN-AFRICA) in the management of snakebite envenomation in sub-Saharan Africa: Clinical studies and actual use since its introduction in 2012

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1. INTRODUCTION & BACKGROUND:

1.1. Objective of this review

Snakebite envenomation (SBE) is a serious health issue mostly affecting poor population in tropical regions. In sub-Saharan Africa, the number of SBE was estimated to be over 300 000 leading to more than 7000 deaths and up to 14 000 victims with disabilities each year (1). Antivenoms are the only specific treatment of SBE. However, there is lack of information and fear to use antivenoms among health care providers in sub-Saharan Africa. Indeed, the reputation of antivenoms has been damaged by the safety risk associated to the use of the first generation and the uncertain quality and specificity of some antivenoms still available in sub-Saharan Africa. In the past decades, the development of new antivenoms have benefited from the major advances in applied biochemistry and immunology. This was successfully achieved with the design of Inoserp™ PAN-AFRICA, a polyvalent antivenom covering most of the medically important snake species of sub-Saharan Africa. The objective of this review is to provide the most comprehensive profile of the clinical efficacy and safety of Inoserp™ PAN-AFRICA to health care providers, researchers, decision makers and any people involved in SBE management in sub-Saharan Africa.

1.2. Use of Inoserp™ PAN-AFRICA in sub-Saharan Africa

Since 2012, Inoserp™ PAN-AFRICA has been used in more than 20 countries from west to east Africa as detailed in Table 1 hereafter. Over 200 000 vials of Inoserp™ PAN-AFRICA have been distributed mainly through marketing approval, special import permit but also through organizations such as armies or NGOs.

Table 1. Geographic distribution of the use of Inoserp™ PAN-AFRICA.

West Africa: ***Benin, Burkina Faso, Ghana, Guinea, Ivory Coast, Mali, Niger, Senegal, Sierra Leone, Togo***	
Central Africa: *Cameroon, Central African Republic, Chad, Equatorial Guinea, Gabon, Republic of Congo*	
East Africa: *Djibouti, Kenya, Sudan, Tanzania, Uganda*	
Southern Africa: *Angola, Zambia*	

1.3. Specificities of Inoserp™ PAN-AFRICA

Inoserp™ PAN-AFRICA is composed of equine origin F(ab')$_2$ immunoglobulin fragments. Following the hyperimmunization phase, immunoglobulins raised against the different venom components are collected and digested by enzymes into F(ab')$_2$ fragments. As recommended by WHO guidelines (2), F(ab')$_2$ present several advantages: In contrast to complete IgG, F(ab')$_2$ have a better safety profile as they do not contain Fc fragments known to trigger side effects. F(ab')$_2$ benefit also from a better pharmacokinetic profile than Fab fragments that are eliminated very quickly from the body. One of the major characteristics of Inoserp™ PAN-AFRICA is that it is highly purified thanks to a specific manufacturing process developed by Inosan Biopharma. Following a series of fractionation and filtration process, the level of F(ab')$_2$ reaches over 95% of the composition of the antivenom (3). In addition, the manufacturing process is performed in perfectly closed conditions, with sterility and microbiology controls carried out regularly throughout the entire manufacturing process. Therefore, antivenoms manufactured by Inosan Biopharma meet viral safety requirement, do not contain pyrogen agents and are preservatives free. Another key feature of Inoserp™ PAN-AFRICA is that it contains highly specific F(ab')$_2$. This means that there is a high proportion of effective F(ab')$_2$ capable to specifically bind to the toxic components of the venoms and neutralize them. Therefore, Inoserp™ PAN-AFRICA can neutralize more venom with less proteins (3). This high-yield production process enables the inclusion of antibodies of additional species in the same vial for a broader coverage. In fact, Inoserp™ PAN-AFRICA is polyvalent and covers all species that are medically important (WHO category 1) in sub-Saharan Africa (4), as detailed in Table 2 hereafter. Finally, Inoserp™ PAN-AFRICA is lyophilized which makes its transport and storage easy and inexpensive as it is not cold chain dependent, which is a decisive asset in tropical regions such as in sub-Saharan Africa.

Table 2. Main characteristics of Inoserp™ PAN-AFRICA.

IgG type	**F(ab')$_2$ (equine)**
F(ab')^2	Over 95%
Protein	Less than 10%
Preservatives	None

Species coverage	**Viperidae:** Cerastes cerastes, Echis ocellatus, Echis leucogaster, Echis pyramidum, Bitis arietans, Bitis rhinoceros, Bitis nasicornis, Bitis gabonica **Elapidae:** Dendroaspis polylepis, Dendroaspis viridis, Dendroaspis angusticeps, Dendroaspis jamesoni, Naja anchieta , Naja annulifera, Naja ashei, Naja nigricollis, Naja haje, Naja katiensis, Naja melanoleuca, Naja mossambica , Naja nubiae, Naja pallida and Naja senegalensis. **Atractaspididae:** Atractaspis irregularis **Colubridae:** Dispolidus typus
Formulation	Lyophilized
Storage	Up to 30°C with possible excursions up to 40°C for reduced period

2. METHODOLOGY

This review presents all clinical data available on the use of Inoserp™ PAN-AFRICA in sub-Saharan Africa since it has been introduced in 2012. The main source of data comes from the clinical studies that have been performed and published but also from all other available source such as published report of patient cases and the most updated pharmacovigilance surveillance report. Four clinical studies have been performed in 5 countries of West and Central Africa, encompassing 22 clinical sites and involving 676 patients as summarized in Table 3 and detailed below:

Evaluation of a new polyvalent antivenom against snakebite envenomation (Inoserp™ PAN-AFRICA) in two different epidemiological settings: Northern Benin and Maritime Guinea (Chippaux et Al, 2015) (5): This is the first clinical study performed with overall 209 patients treated. The study objective was to evaluate the clinical efficacy and safety of Inoserp™ PAN-AFRICA in 2 countries with different SBE profile: North Benin where Echis ocellatus represents 75% of envenomation and Maritime Guinea well known for a high incidence of elapids bites (Naja and Dendroaspis gender).

Antivenom serotherapy in Mali: experience at Kati reference health center, Kouligoro region (Coulibaly et Al, 2018) (6): This single center observational study was performed on 154 patients in a health center in west Mali with the objective to assess the clinical efficacy and safety of Inoserp™ PAN-AFRICA in a region with high incidence of *Echis ocellatus* bites.

Evaluation of the efficacy and tolerance of Inoserp™ PAN-AFRICA in Senegal (Lam et Al, 2019) (7): this cohort multicenter study was performed on 63 patients in Senegal. The objective was to evaluate the safety and efficacy of Inoserp™ PAN-AFRICA under realistic conditions at rural health facilities experiencing cytotoxic, hemotoxic and neurotoxic envenomation.

Snakebites in Cameroon: evaluation of snake antivenom in Africa (ESAA) and real-life conditions (Chippaux et Al, 2022) (8): This is the largest multicenter clinical study performed with Inoserp™ PAN-AFRICA**.** Overall, 250 patients have been treated in 14 clinical sites in Cameroon. The main objective was to study the short and mid-term safety and efficacy profile of the antivenom in real condition.

Table 3. Characteristics of clinical studies involving Inoserp™ PAN-AFRICA.

Study reference	Design	Countries	Number of clinical sites	Nb of patients treated
Chippaux et Al, 2015 (5)	Multicenter prospective clinical study	Benin Guinea	3	209
Coulibaly et Al, 2018 (6)	Monocenter prospective observational study	Mali	1	154
Lam et Al, 2019 (7)	Multicenter prospective cohort study	Senegal	4	63
Chippaux et al, 2022 (8)	Multicenter prospective clinical study	Cameroon	14	250
Overall statistics on clinical studies		5 countries	22 clinical sites	676 patients

In addition, several publications reporting the use of Inoserp™ PAN-AFRICA in patients have been identified: 1 patient presenting with neurotoxic envenomation in Guinea (9), 1 patient bitten by a carpet viper (Echis ocellatus) in Togo (10) and 1 herpetologist bitten by a puff adder (Bitis arietans) in Guinea (11).

Finally, Inosan Biopharma maintains a pharmacovigilance surveillance of the use Inoserp™ PAN-AFRICA worldwide and compiles an updated Periodic Safety Update Report (PSUR) each year. The last PSUR used for the review is dated of February 28, 2022, and encompasses reports received from 2013 to December 2021.

3. RESULTS:

3.1. Clinical studies:

3.1.1. Demographic characteristics and SBE syndromes

In most cases, patients included were young male adults with a median age from 18 years in Benin to 38 years in Mali and a sex ratio (M/F) from 2.7 in Senegal to 4.5 in Benin. Most patients presented with hemorrhagic syndrome (up to 93% in Cameroon), however 2 studies reported more than 10% of neurotoxic syndromes (Guinea and Senegal). Echis ocellatus was the species involved in most hemorrhagic syndrome cases. However, when it was feasible, other species have been identified such as Bitis arietans (Cameroon), Naja melanoleuca (Cameroon), Dendroaspsis viridis (Guinea), Dendroaspsis polylepis (Guinea), Dendroaspsis jamesoni (Cameroon) and Atractaspis species (Cameroon). The severity of envenomation varied from mild (grade 1) to serious (grade 4) according to the ASV severity score (12). Patients could present rather quickly (4h50 of median time in Cameroon) to lately (24h of median time in Benin or in Senegal hospitals) after snake bite. See details in Table 4 hereafter.

Table 4. Demographic characteristics and SBE syndromes.

Study reference	Country	Age median (Q25%-Q75%)	Sex-ratio (M/F)	SBE syndromes % hemorrhagic (Including positive WBTC) (1)	SBE syndromes % neurotoxic	Time from snake bite to admission (median)
Chippaux et Al, 2015 [5]	Benin (n=100)	18 [13-29]	4.5	90%	2%	24h
	Guinea (n=109)	30 [19-41]	3	88%	12%	6h
Coulibaly et Al, 2018 [6]	Mali (n=154)	38 NA	3.7	82%	NA (2)	NA (2)
Lam et Al, 2019 [7]	Senegal (n=63)	22 [13-35]	2.7	38%	13%	6h (Health Unit) 24h (Hospital)
Chippaux et al, 2022 [8]	Cameroon (n=250)	25 [14- 50]	NA (2)	93% (3)	9% (3)	4h50

[1] WBTC=Whole Blood Clotting Test; [2] NA=Not Available; [3] Some patients presented both hemorrhagic and neurotoxic syndromes.

3.1.2. Efficacy & safety profile

The mean number of vials administered was consistent from a study to another ranging from 1.4 to 2 per patient except in Cameroon where patients got 3.2 vials in average. The length of hospitalization varied from 1.6 to 5.8 days in average but could largely be influenced by local practices. Global lethality rate was low (2.5%) and was often associated with delayed treatment or neurologic syndromes. Adverse events, mostly of mild or moderate intensity, were reported in 5 to 11% of patients. See details in Table 5 hereafter.

Table 5. Efficacy & safety profile.

Study reference	Country	Number of vials per patient (mean)	Length (days) of hospitalization (mean)	Lethality	Adverse events
Chippaux et Al, 2015 [5]	Benin (n=100)	1.8	5.8	3 (3%)	11 (11%)
	Guinea (n=109)	1.4	4.5	1 (1%)	6 (5.5%)
Coulibaly et Al, 2018 [6]	Mali (n=154)	2	1 to 5 (Min-Max)	0 (0%)	14 (6.5%)
Lam et Al, 2019 [7]	Senegal (n=63)	1.4	1.6	2 (3.2%)	3 (4.8%)
Chippaux et al, 2022 [8]	Cameroon (n=250)	3.2	NA [1]	11 (4.4%)	NA [1]

[1]NA=Not Available.

3.2. Supporting data:

3.2.1. Published patient cases

Among the 3 patient cases published, there were 2 adult women (including one who was breastfeeding) and 1 man who was 64 years old. SBE involved 3 different species: Dendroaspis gender, Echis ocellatus and Bitis arietans. In all cases, the antivenom was taken rather rapidly (less than 6 hours) and 4 to 6 vials were administered depending on the case. All patients gradually improved without sequela. No side effect was reported.

3.2.2. Pharmacovigilance surveillance

According to the spontaneous sources and literature, 17 non-serious and 23 serious adverse events have been reported since 2012 to Inosan Biopharma. These safety reports are consistent with the safety profile specified in the approved product information. Based on all safety information available to date, Inoserp™ PAN-AFRICA has a positive risk-benefit profile.

4. DISCUSSION

In a recent review of antivenoms available in sub-Saharan Africa (13), the authors conclude that there is a lack of good quality clinical data. This current review aims to fulfill this critical gap. According to this current review, Inoserp™ PAN-AFRICA is safe and effective in treating snakebite victims. However, some limitations are associated to this review: For feasibility reasons, the clinical studies reported were not designed as comparative randomized studies. Also, the proportion of elapids' bites remains low in comparison to vipers' bites, reflecting the actual epidemiology in the region. Finally, the number of pharmacovigilance cases is clearly under reported as this may not be part of medical routine in many health centers in Africa.

5. CONCLUSION

This review summarizes all clinical data on Inoserp™ PAN-AFRICA after 10 years of use. With an estimated number of 200 000 vials distributed in over 20 countries and 4 prospective clinical studies performed in 5 countries, Inoserp™ PAN-AFRICA benefits from a large clinical experience in sub-Saharan Africa. All clinical information available consistently indicate that Inoserp™ PAN-AFRICA effectively control envenomation symptoms with an excellent safety profile.

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